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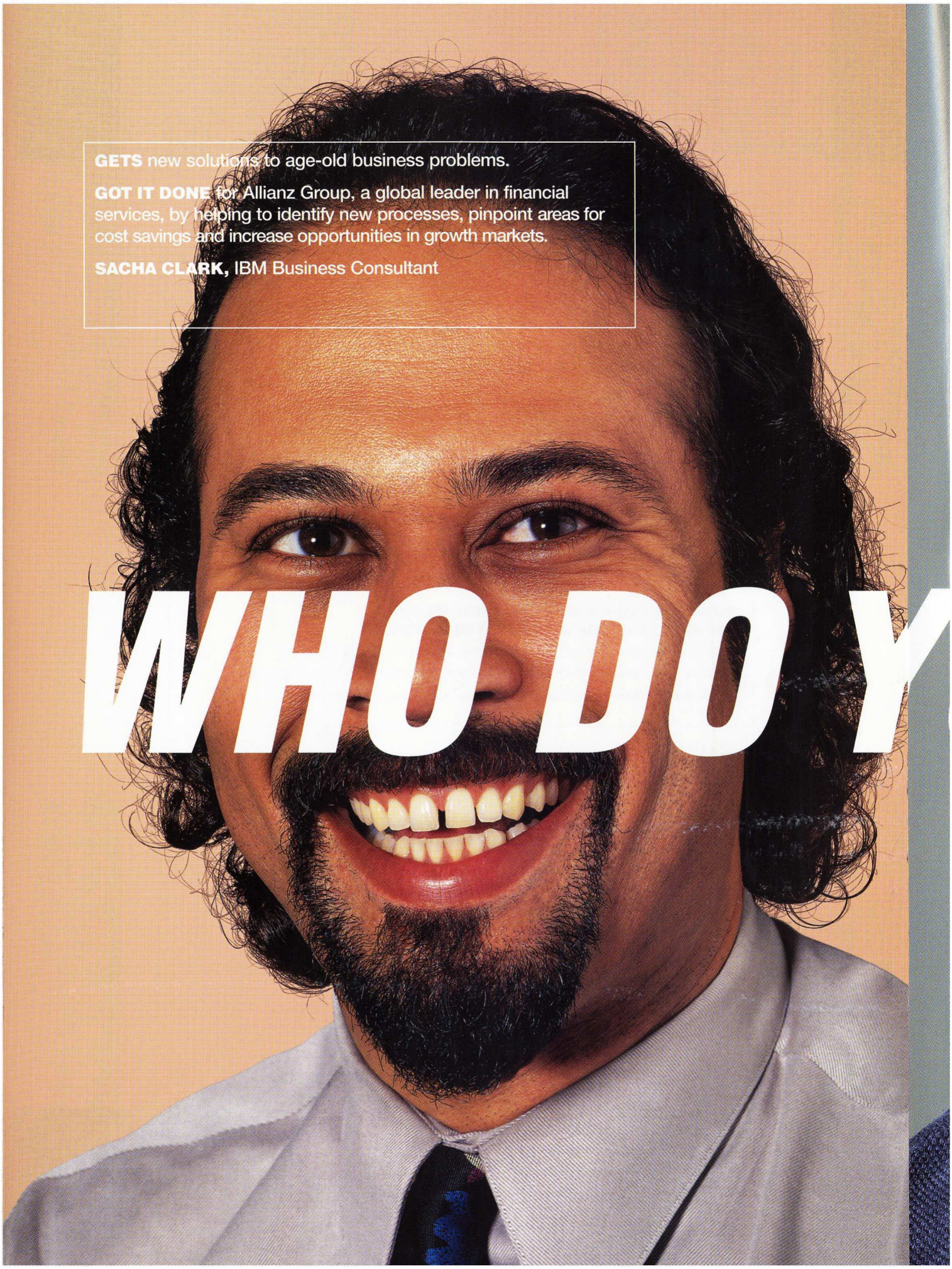
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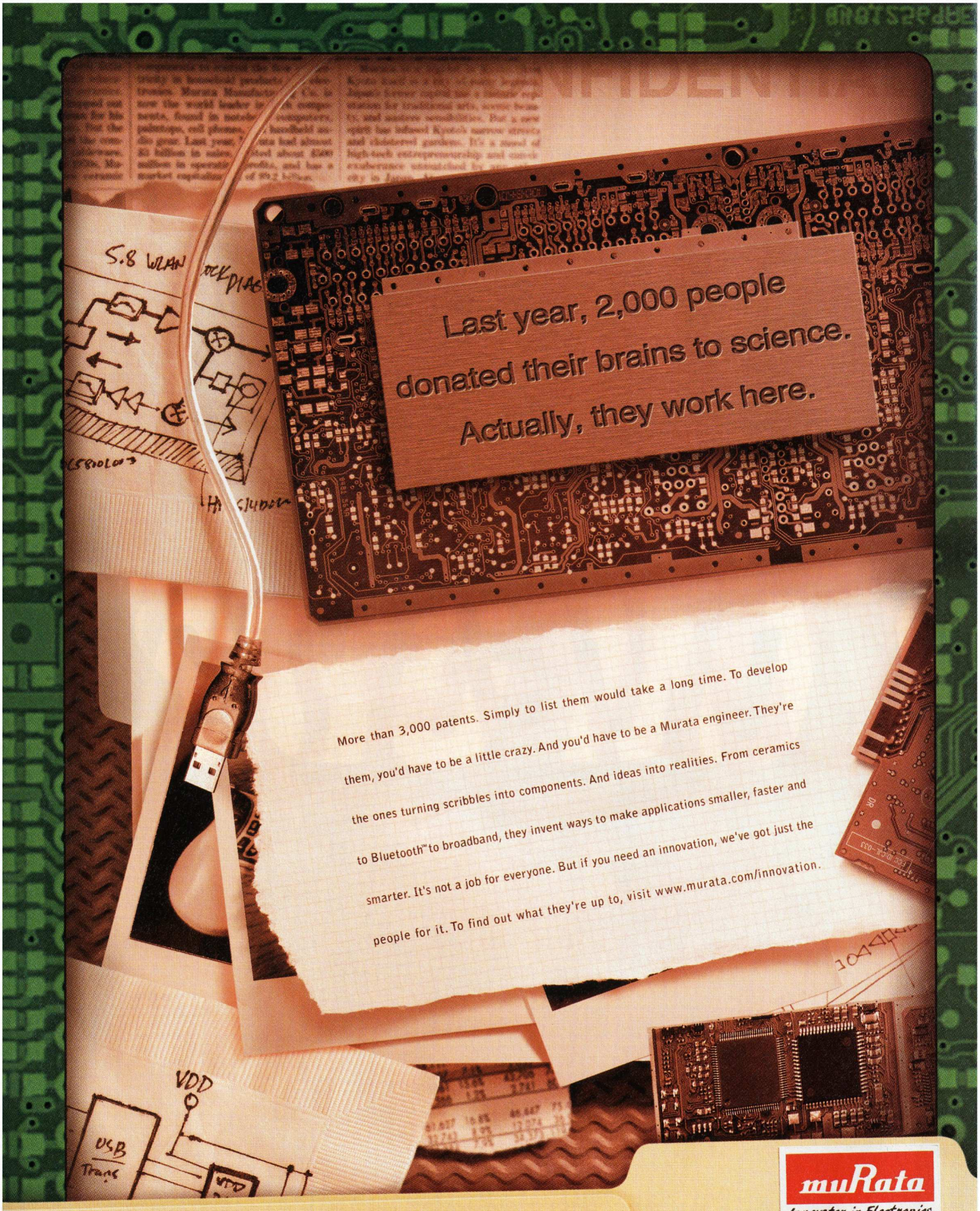
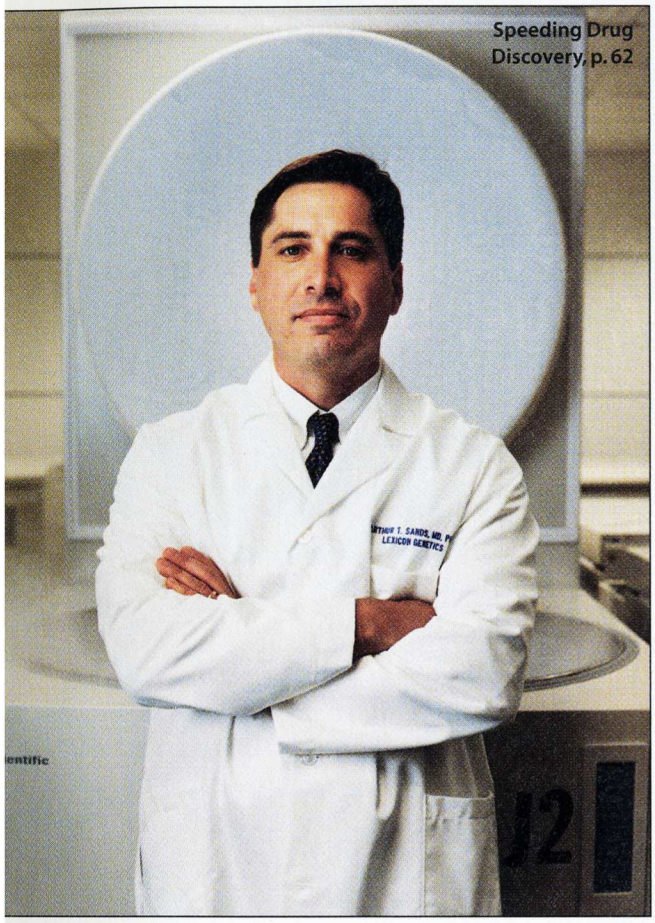
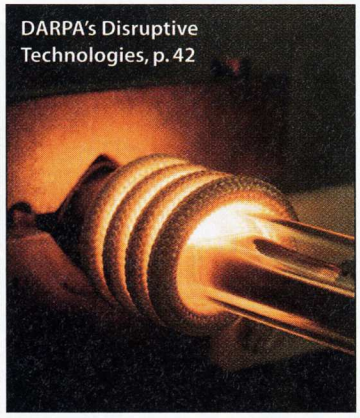
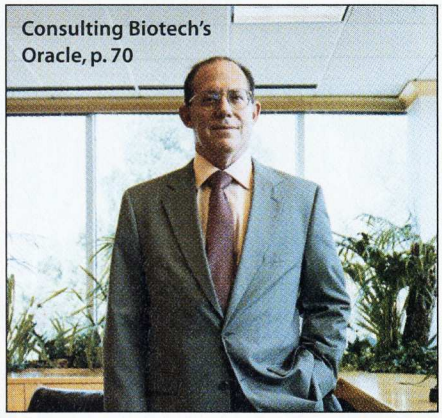
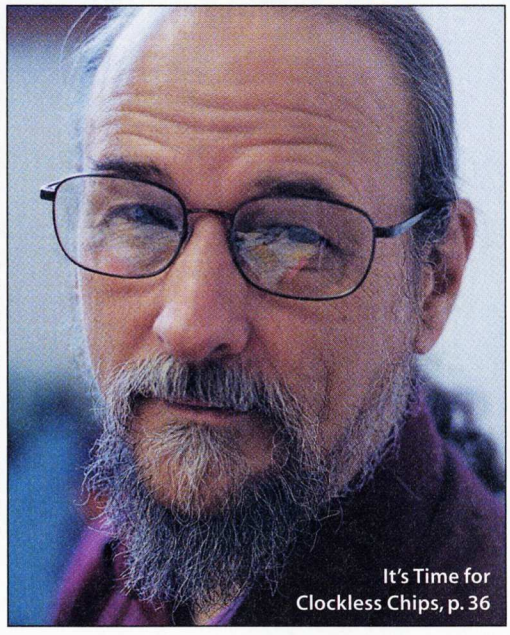


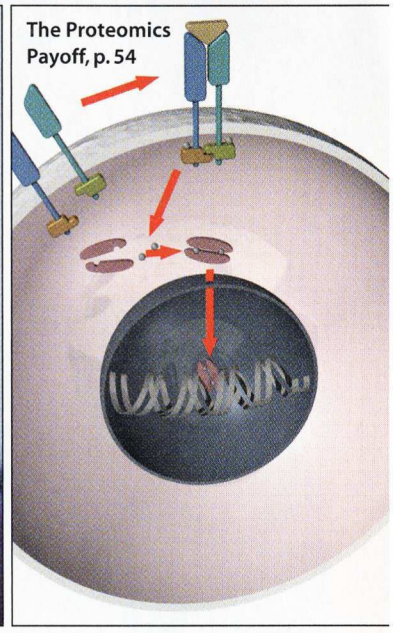
CONTENTS











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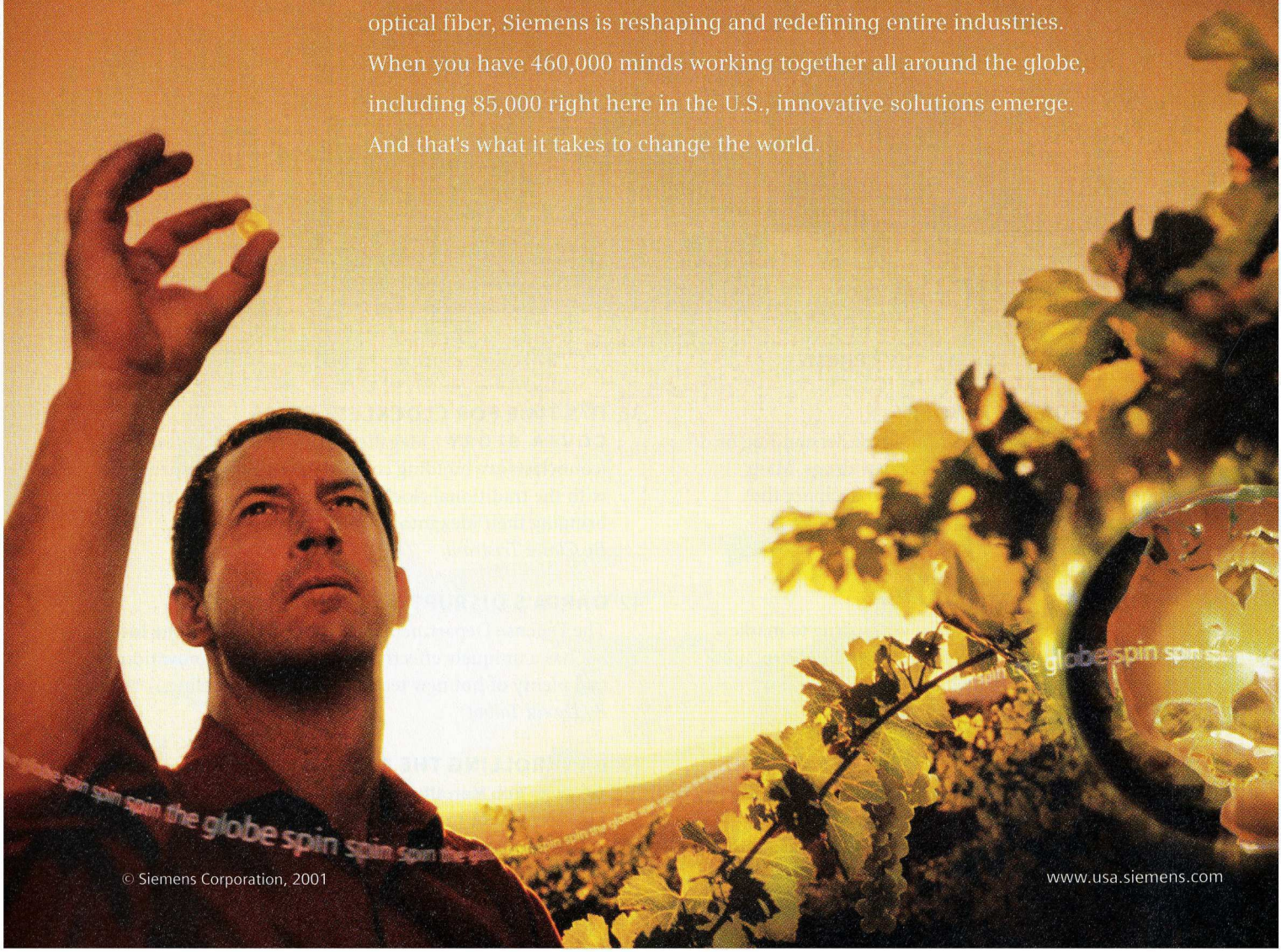

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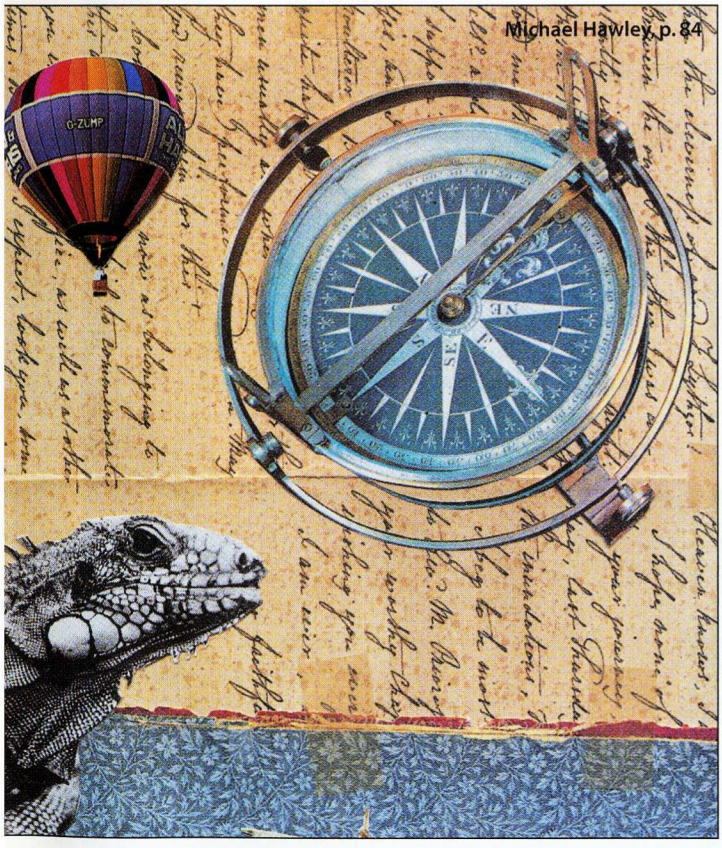
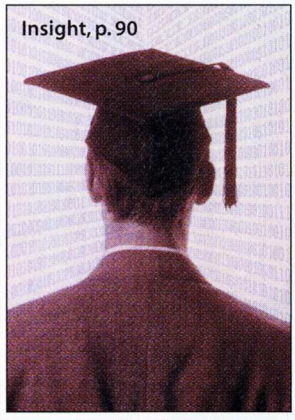
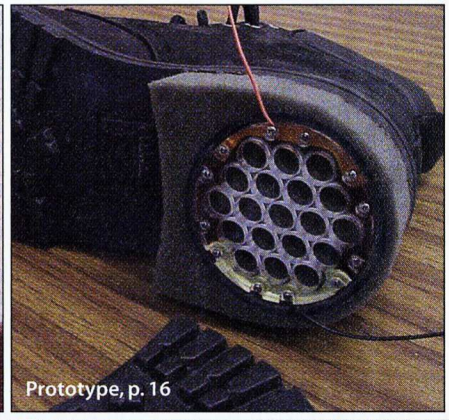
CONTENTS

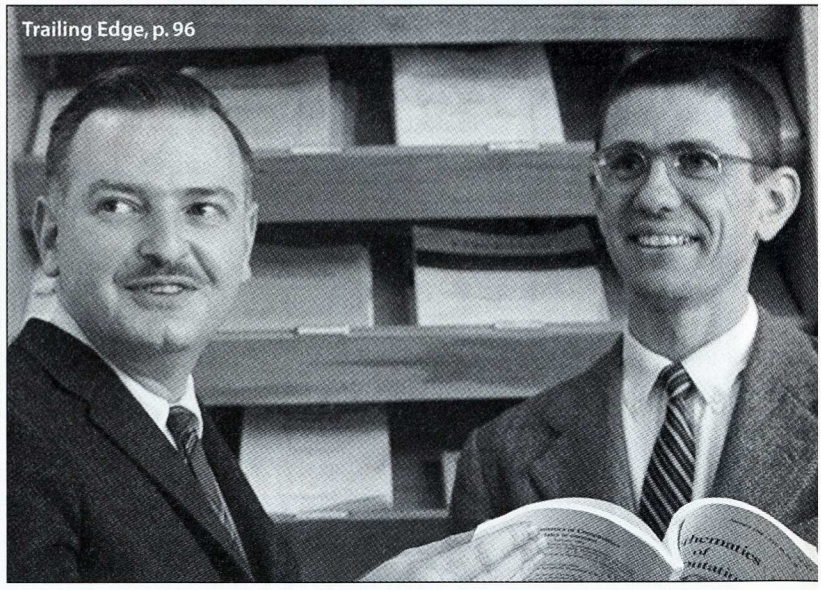
DEPARTMENTS

COLUMNS







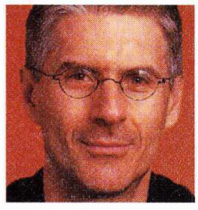


THE HUMAN PROTEOME

Technology these days is moving so quickly that entire new areas of research and the accompanying markets spring up within a few years. Take what is now called the human "proteome." By the sound of it, you might guess that it has something to do with the genome. And if you know biotech, you realize that it's one of the hottest fields these days for big companies and startups alike: the identification of all the proteins in our cells and the analysis of their significant interactions.

What you might not know, even if you're a biotech insider, is how the name originated. As Jon Cohen tells us in "The Proteomics Payoff" *(p. 54)*, before mid-1994, the word "proteome" didn't exist. It was then that Marc Wilkins, a student at Macquarie University in Sydney, Australia, was looking for the right term to describe the full array of human proteins. These are the workhorses of the cell and potential targets for new drugs. Genes are blueprints for the construction of proteins. But identifying and sequencing the genes—the monumental task undertaken by the Human Genome Project—doesn't provide enough data to develop new therapies.

In a scientific paper written to support his doctoral thesis, Wilkins kept having to write the clumsy phrase "all proteins expressed by a genome." After trying a couple of other contenders that failed to roll off the tongue, he settled on "proteome." In September 1994, Wilkins used the new coinage at a scientific conference in Italy. His audience bought it.



And now others are buying. Since June 2000, venture capitalists and stock offerings have pumped more than $700 million into proteomics companies. Genomics companies and big pharmaceutical firms are starting their own proteomics divisions. More than 70 companies are now attacking some piece of the proteomics problem, each with a specific technology and angle of approach.

The job won't be easy. There are more proteins than genes. And the proteomics payoff will come only with an understanding of the tangled network of interactions among proteins. There is still a long way to go. But Cohen portrays feverish activity in this young field, activity that should up the chances of reaching the payoff.

In one sense, though, proteomics may be part of the problem, as well as part of the solution. The genome project, and now the worldwide, informal "proteome project," are piling up data faster than companies can deal with it. The process of bringing a new drug to market is already long and expensive. Will the mountain of new information present an obstacle that slows drug development even more? That's the question Gary Taubes asks in "Speeding Drug Discovery" *(p. 62)*. Taubes tells us that there are, in fact, many new approaches to breaking the drug development bottleneck. He highlights three that he considers the most promising.

To complete this special report on where biotech stands now that the genome has been deciphered, we add an element that is always important in our coverage of emerging technology: personality. Cohen returns with a backstage look at the most controversial impresario in biotech: William Haseltine, CEO of Human Genome Sciences. Depending on your point of vantage, Haseltine is either a genius or a self-serving blowhard. Cohen shows both sides of this complex personality—and then lets you draw your own conclusions.

Indeed, in general we let you decide for yourself how significant the field of proteomics will be. But as always, we tell you what the new technology is, how it works and why it matters—just the information and analysis you need to draw conclusions you can have confidence in. —*John Benditt*

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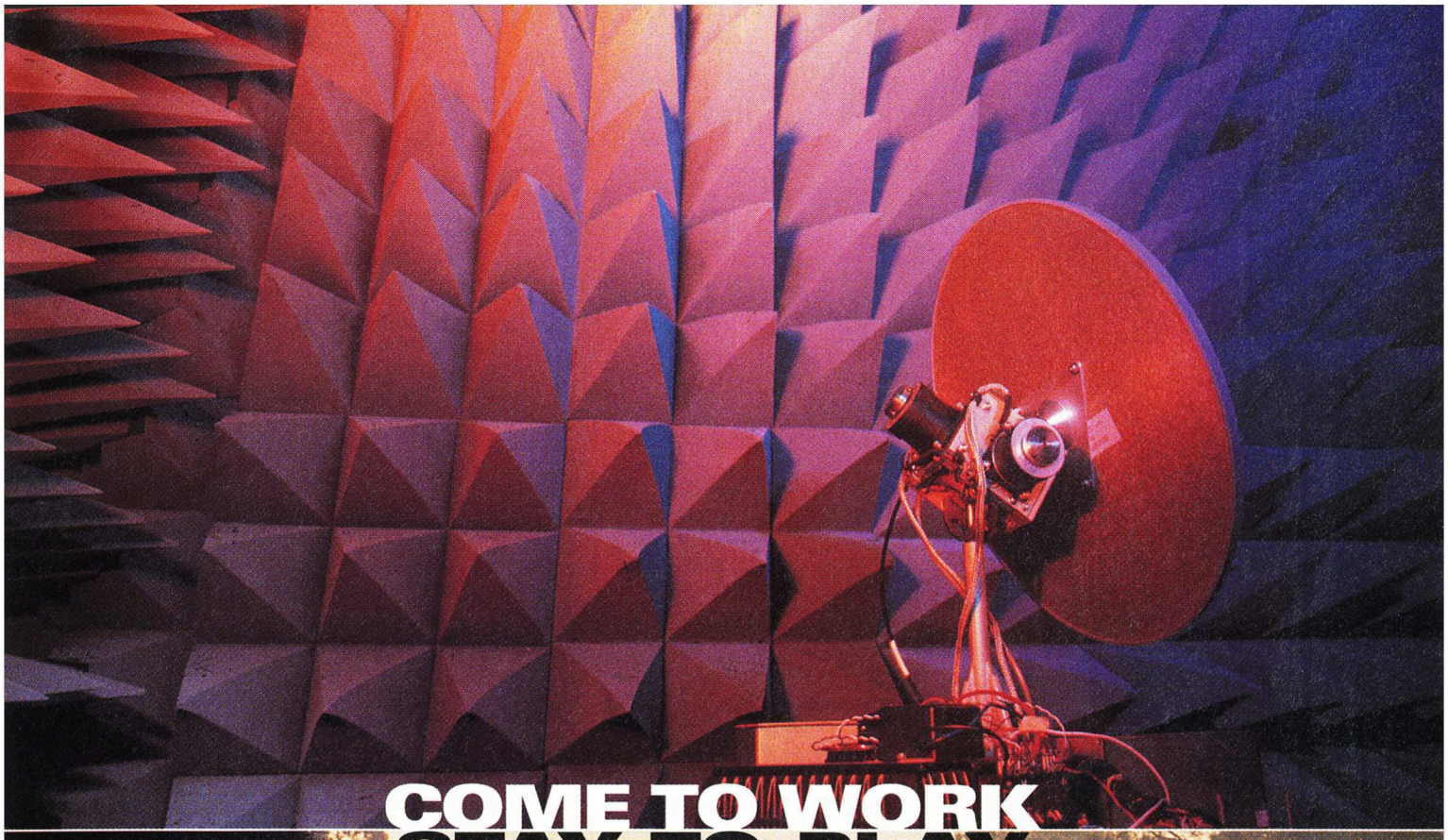

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FEEDBACK

LETTERS FROM OUR READERS

BUILDING SOLUTIONS

I disagree with Michael Hawley's portrayal of the California power crisis ("Edifice Complex," *TR* July/August 2001). The crisis is not an issue simply of conservation, but of mismanagement and myopia. For decades, expansion of California's energy infrastructure has been railroaded by well-meaning but misguided environmental groups. No new nuclear or coal-fired power plants have been sited in the last two decades, and existing plants have been taken off line. Yet California's population has risen by almost 75 percent in the last three decades. So even though California's energy consumption per capita is one of the lowest in the nation, there still isn't enough energy to go around. It is not clear how "small changes in consumer behavior" could have prevented this unfortunate situation.

Billions of dollars in default, California's utilities are unable to supply their customers with power not because of President George W. Bush's alleged hostility toward conservation, but because of shortsighted pricing policies and misinformed environmental lobbies preventing technological growth. The solution to the energy crisis will not be found in conservation alone, but in the combined efforts of consumers demanding less, providers supplying more, and legislators letting a free market determine the price.

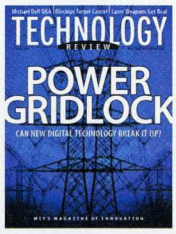
Peter Cress
Loma Linda, CA

Michael Hawley's column only touches on a small part of the problem of getting intelligent architecture into the mainstream. Cost is a big factor, of course, but the potential savings over time would seem to mitigate that. Surely, insurance for a house that can alert the fire department on its own would be cheaper than for a house without this capability.

The main obstacles lie in the building industry itself, and the supporting building codes. In many places, it is flat out illegal to use innovative house designs. The building codes mandate the allowed materials, methods and techniques used to build a house. If the building codes don't get you, the neighborhood association surely will. Most homeowners don't have the resources to fight city hall on these issues.

Then there are the people who actually build the houses. Construction crews specialize in certain house designs. A "custom" home—one that is not based on a standard design—costs significantly more per square meter. If you want your house built on time, and for a reasonable price, you pick one of the architectures that the builder suggests, with only minor modifications.

Chris J. Kiick
Dallas, TX



"The main obstacles to intelligent architecture lie in the building industry itself. If the codes don't get you, the neighborhood association surely will."

GRIDLOCK

Peter Fairley's article on Gridlock ("A Smarter Power Grid," *TR* July/August 2001) is a milestone achievement, explaining how the crisis came about and why the problem is not going away. But the question remains: who is going to step up and fix the problem? Even if the technology is there—fuel cells to augment the grid and protect certain sectors from breaking down, or electronics to manage the grid—who is going to pull it all together and prevent the kinds of things that Mr. Fairley points out? Free market competition, as much as we respect it, comes up short on this issue because there is no profit motive in the existing system.

William D. Montjoye
San Antonio, TX

As alternative energy sources and distributed generation become more of a reality, why isn't anyone talking about replacing the power-consuming AC/AC, AC/DC and DC/AC transformers, converters and inverters with direct current?

Today, we lose millions of ergs of energy daily through heat, core losses and magnetic flux when transforming energy. Yet a microgenerator, fuel cell or solar-powered device generating DC power could easily supply energy to household electronic devices. A simple "smart" plug with variable resistors could reduce energy waste. Edison, after all this time, may be proven right.

Samuel A. Brown
Chula Vista, CA

FATHERING BITS

Claude Shannon had remarkable insight ("Claude Shannon: Reluctant Father of the Digital Age," *TR* July/ August 2001). He not only laid the groundwork for electrical transmission of intelligence, but also for any kind of digital description and transfer of intelligence. Wouldn't it be something if he were here today to lend his expertise to the human genome sequencing efforts? The life encoded in DNA and its associated chemistry have redundancy and error-correcting characteristics, in addition to recording, reading and duplicating capabilities. Shannon could give a wonderful analysis as to how a digital

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code of about three billion chemical units, which includes perhaps 30,000 unique sequences of code (our genes), is capable of completely describing a human being.

Art Hughes
Gladwyne, PA

Your encomium to the late Claude Shannon effectively summarized his numerous contributions to information and communications systems theory. I was surprised, however, to note the omission of one well-known contribution: the Shannon Sampling Theorem. Around 1950, this principle served as a cornerstone for the analysis and design of early sampled-data control and communications systems (the analog predecessors of today's digital systems); it surely deserved mention in your summary of his fundamental contributions.

Philip J. Bonomo
Silver Spring, MD

M. Mitchell Waldrop responds:
Philip Bonomo is quite right that the Sampling Theorem is one of Shannon's critical contributions to communications theory. Indeed, it's one of the main reasons why we're currently digitizing just about every form of information imaginable. For example, the theorem explains how a continuous signal like a sound wave can be encoded as a series of discrete ones and zeroes on a CD, or in an MP3 file, and then reconstructed with seemingly perfect fidelity: as long as the encoding process is fast enough when it measures, or "samples," the original signal, the errors in the reconstruction will be beyond the range of human hearing. (More formally, a continuous signal of finite bandwidth can be reconstructed perfectly if the samples are taken at at least twice the bandwidth frequency.)

That said, however, an account of all of Shannon's fundamental contributions to communications theory easily could have filled an entire issue of *Technology Review*. And in this case, as Shannon himself noted in his original 1949 article (in volume 37 of *Proceedings of the Institute of Radio Engineers*), the Sampling Theorem

had been proved by others long before. He was the first to recognize its importance to communication, which was no small matter. But since choices had to be made, I rightly or wrongly decided to leave it out, and focus instead on Shannon's truly original contributions.

DELL'S MARKET

Your interview with Michael Dell ("Direct from Dell," *TR* July/August 2001) does a disservice to the concept of innovation. Dell's self-serving statements seem aimed at conflating minor late-development processes with true innovation. This makes Dell Computer appear more like a technology company than the packager and shipper it actually is. Dell's sole example of in-house innovation was the "risky" idea of putting a 38-centimeter screen in a laptop, which he claimed was technologically difficult. If this is real innovation, then why do many other major PC vendors also sell laptops with 38-centimeter screens? Why not interview those other CEOs to learn how their companies were able to think up such mind-bending inventions?

Michael Lin
Boston, MA

What I found most interesting about Dell's comments was that he saw his company as thriving on information, not technology, and that he is a provider of systems and customized "solutions" rather than of standard productions. That is what makes Dell Computer revolutionary and different from the Fords, the Rockefellers and even the Gateses of the world.

Scott Anderson
Washington, DC

DEFENDING LIGHT

I read David H. Freedman's excellent article with interest ("The Light Brigade," *TR* July/August 2001). However, the author doesn't discuss the potential use of reflective materials as a defense against this technology. Freedman does mention battlefield conditions, such as smoke and physical obstacles, that could diminish the effectiveness of ground-based implementations. But a more serious issue would involve highly reflective materials that could be deployed as surface covering or chaff to disperse a beam, or as controllable mirrors designed for the express purpose of redirecting beams, possibly against their own sources. This seems such an obvious defense against a weapon based on light. Is this type of defense of any concern to the manufacturers of these weapons, and has any research been done in this area?

Ron Pacheco
Brookfield, CT

David H. Freedman responds:
Thanks for bringing this up. Yes, reflective coatings are one of several possible laser countermeasures that the military has been studying in depth for years. There are, in fact, reflective coatings that are so effective that far less than one percent of the beam's energy is absorbed by the surface, protecting the surface (and whatever lies beneath it) from damage. But such coatings are not likely to be a factor in real-world conditions for several reasons.

For one thing, high-quality reflective coatings are extremely difficult and expensive to apply, especially to large or complexly shaped surfaces. For another, the battlefield wear and tear would quickly degrade these brittle, delicate surfaces. And perhaps most important, even the slightest deposit of dust would render the coating useless, because the dust particles themselves would heat up under the beam and melt the coating; it takes a full clean-room environment to keep a good coating sufficiently dust-free. According to the people who research laser countermeasures, there is currently no way to reliably protect against a megawatt laser.

DVDS UNSCRAMBLED

One thing film companies are not quick to point out is that the act of copying a DVD is independent from the act of decrypting a DVD ("The DVD Rebellion," *TR* July/August 2001). Without the decryption software, anyone can make a bit-by-bit copy of a DVD that would be perfectly readable. Any large illegal shop can copy the master and stamp out new DVDs for only a few dollars per disk, without reading the information on the DVD. The people pressing 500,000 copies of *Star Wars: Episode I* in a warehouse are the criminals, not the kid who wants to watch the movie he just bought at Tower Records for $29.

Eric D. Mudama
Boulder, CO

"Michael Dell's self-serving statements make Dell Computer appear more like a technology company than the packager and shipper it actually is."

Simson Garfinkel responds:
Alas, the recording industry already thought of this attack, and they've beaten you with a preemptive strike. You cannot simply make a "bit-by-bit copy" of a commercial DVD on a burnable DVD (also know as a "DVD-RAM"). Every DVD-RAM sold is prerecorded with a message to the DVD player that says, "If you find an encrypted movie on this disk, don't play it." Consumer DVD players look for this message; if they find it, they won't play an encrypted movie. So your bit-by-bit copy won't work; it will have the prerecorded message, and the DVD player will refuse to play.

The DeCSS program lets you defeat this prerecorded message. Instead of storing an encrypted movie on your DVD-RAM, you actually store the unencrypted MPEG-2 files. Most consumer DVD players will play DVD-RAMs that have MPEG-2 files on them, since this is the way that consumers are supposed to be able to make DVDs from their home movies one day in the near future.

So it turns out that DeCSS really does enable DVD piracy, just as the industry says it does!

Sorry that I didn't make this clear in the original article. The finer points of DVD copy protection are really complicated and, truth be told, only interesting to us geeks.

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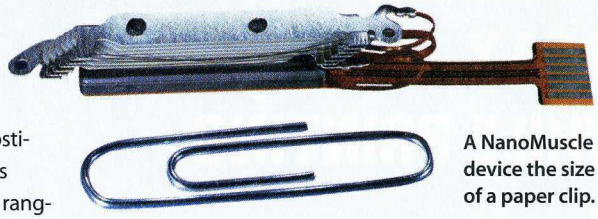


A NanoMuscle device the size of a paper clip.

Inexpensive, matchstick-sized devices with no moving parts could serve as cheap, power-efficient substitutes for small electric motors found in consumer products ranging from microwave ovens to cars. These devices—under development by NanoMuscle in Antioch, CA—translate electronic signals into linear motion without the need for bulky magnets, coils, spindles and position sensors. The devices consist of off-the-shelf microprocessors attached to small metal strips, which are connected with wires made of shape memory alloy. (This alloy, used in most cell-phone antennas, changes shape in response to an electrical signal.) In the devices, proprietary software regulates the processor's electrical signal to achieve a given effect—say, to close a doll's eyes halfway.

Once production ramps up, the nanomuscles should cost a few dollars each, according to NanoMuscle CEO Rod MacGregor. NanoMuscle has already made headway in the toy market. Hasbro will be using the devices in toys that will be in stores as soon as Christmas 2002. The company has five patents pending; mass production started in August.

ICY FLIGHT

When American Eagle flight 4184 crashed near Roselawn, IN, in 1994, having accumulated a fatal amount of ice on its wings, aeronautics engineer Michael Bragg set out to make sure such accidents didn't happen again. Bragg and his team at the University of Illinois at Urbana-Champaign have since developed a smart icing system that does more than just alert the pilot when ice accumulates on the plane, as current instruments do. Sensors characterize how the ice buildup on the wings or tail is affecting the plane's aerodynamics. If onboard heaters can't melt away all the ice, Bragg's system will tell the pilot how to compensate to maintain control and stability. The system consists of neural-network-based software that collects information from the sensors and translates the data into particular actions. Eventually, Bragg says, the technology will be able to automatically adjust the plane's speed or wing-flap position. Bragg's team recently conducted computer simulations and is preparing to flight test the system this winter.

DIGITAL FUN BOX

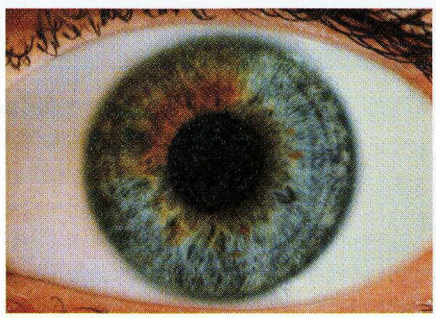
Researchers at IBM's Almaden Research Center in San Jose, CA, are developing a device that could consolidate all of our digital media in a single 150-gigabyte box. You'll be able tap into the device, which IBM calls Casa, through your TV, laptop, handheld or any other digital player.

Casa will convert a file to whatever format is needed to play it on a given device. Songs from CDs, for example, will convert themselves to MP3 music files when you access them from an MP3 player. Digital photos will automatically adjust their quality based on the type of screen you're looking at them on. IBM is building a prototype and projects commercialization in two to five years.

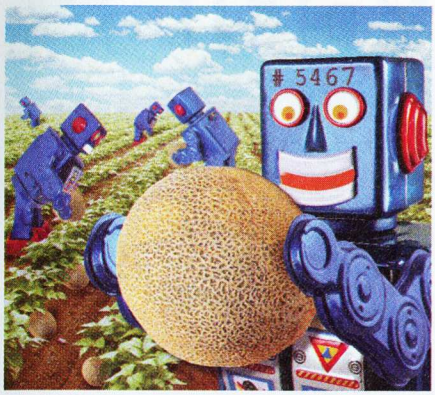
PUPILS TO THE TEST

Urine and blood tests can usually only detect substances consumed in the past two to three days. A new technique, devised by Iritech in San Jose, CA, screens for longer-term drug use—up to two weeks—by looking at eye response. A person looks into a binocular-like camera and is exposed to a flash of light. Software calculates how quickly the pupils shrink and recover, compares this response against pupil records stored in a database, and gauges within seconds whether the subject has taken drugs or alcohol during the past several weeks.

Iritech CEO Daniel Daehoon Kim says the test would be best suited as a screening tool for prisons or for employers evaluating job applicants. One possible drawback: some legitimate medications, such as antiseizure drugs, affect pupil response and could cause false positives. The technology is 95 percent accurate, based on clinical studies involving more than 12,000 subjects. The company hopes to give the system its first real-world test this year at a prison in Santa Clara, CA.



STONE (EYEBALL); AP PHOTO ARCHIVE (DE-ICING); SUSAN VOGEL (NANOMUSCLE)



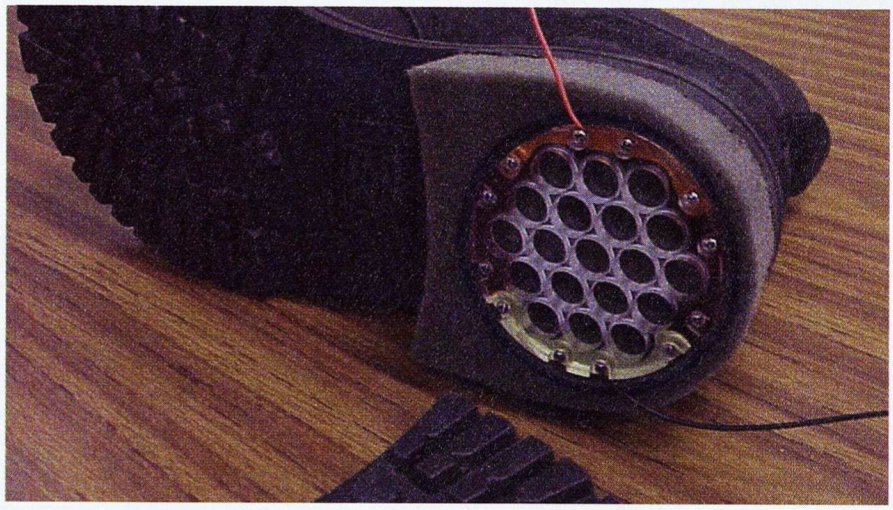
MELON MACHINE

Melon harvesting is hard, tedious work. Now a team of Israeli and U.S. researchers has designed a vision-endowed, melon-picking robot to do the job. The machine consists of a mobile platform on which are mounted an image-processing system, air blowers and a mechanical arm with a gripper attached. As a tractor slowly pulls the platform through the field, cameras take pictures that the system analyzes. (The air blowers ruffle the foliage to expose the fruit.) When the harvester sights a melon bigger than a certain size—and therefore presumed to be ripe—it extends the gripper to grab the fruit and lift it off the ground. Knives connected to the gripper slash the stalk, and the gripper places the melon on a conveyor belt. The robot is the fruit of a collaboration among three Israeli organizations (Ben-Gurion University, the Weizmann Institute of Science and the Agricultural Research Organization) and Purdue University. It could be ready to work the fields in one to two years.

SPIDER-ASSISTED HEALING

Blood-clotting wound dressings are limited by their need for refrigeration and short shelf life: their component proteins tend to break down. Egea Biosciences in San Diego is developing (under Army contract) a compression bandage—the type used for major wounds—coated with a blood-clotting substance that might avoid those limitations.

The dressing is a variant of the fibrinogen that the body produces to promote clotting. A key ingredient is a protein found in spider silk, says Egea CEO Glen A. Evans. This protein could form clots for large wounds that otherwise would continue to bleed. The synthetic powder does not degrade over time or need refrigeration. It is several years from commercial introduction.



POWER WALKING

Taking a vigorous walk tones the muscles; soon it could recharge your personal electronics too. Researchers at SRI International say they've built a boot that can convert 2.5 hours of walking into enough electricity to provide 20 minutes of cell-phone use. The key ingredient is a polymer that generates electricity when flexed. It's one of the so-called dielectric elastomers, which are more rubbery, flex farther and produce much more power than the piezoelectric materials used in earlier attempts at power-generating shoes, says Ronald Pelrine, who heads the SRI project. The U.S. Defense Advanced Research Projects Agency, which is funding SRI's research, is seeking boots that can power electronics like navigation aids. The polymer could also ease the strain of marching by expanding quickly after each step, giving the foot a small boost, Pelrine says. But any shoe-mounted generator has its power limits, he says, beyond which the shoe would become uncomfortable—"like walking in mud."

CLEAN SLATE

The blizzard of chads from last year's presidential election prompted numerous calls for electronic touch-screen voting. But such devices have their own vulnerabilities. In particular, a mere scratch on the sensitive screen can cause a breakdown—and on election day, failure is not an option.

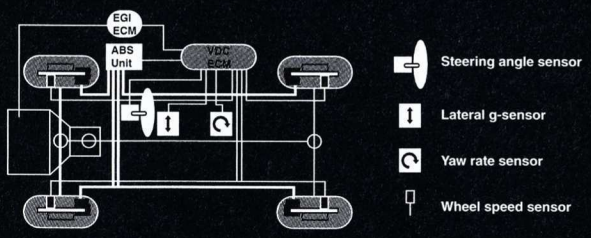
Enter the eSlate, made by Hart InterCivic of Austin, TX. To make a selection, the voter turns a small wheel; there's no need to touch the screen. Neglecting to pick a candidate triggers an alert message; the device also makes it impossible to select multiple candidates for the same office. A voter can review the ballot before officially casting it. The legal-pad-sized eSlate can also be configured to allow voting access for nonreaders and for disabled voters. Texas and Colorado have certified eSlate for use in elections; several other states are reviewing it. Dell Computer has signed on as a distribution and marketing partner.

PHOTOGRAPHS: HART INTERCIVIC (VOTING MACHINE); THE IMAGE BANK (SPIDER WEB); SRI INTERNATIONAL (SHOE); ILLUSTRATION: VITO ALUIA

ENGINEERED TO BE ALMOST PSYCHIC.

Introducing a car so technologically advanced, it can sense trouble and begin to adjust for it before the driver even notices there's a problem. It's the 6-cylinder 212-horsepower Subaru Outback VDC.

The VDC stands for Vehicle Dynamics Control, a highly intelligent stability system that's designed to help prevent loss of control due to conditions like oversteer, understeer, wheel spin or vehicle drift. Ingeniously coupled with full-time Subaru All-Wheel Drive, it rivals systems found in vehicles costing thousands more.



The heart of VDC is a sophisticated series of sensors that continually monitor steering angle, wheel speed, brake pressure, yaw rate and lateral g-forces. The instant a difference is detected between the driver's intended direction of travel and the path the car is actually taking, VDC takes corrective action. Momentary brake pressure may be applied to individual wheels. The All-Wheel Drive system may redistribute the amount of power between the wheels. Even the engine's output may be momentarily reduced. Before the driver even realizes that loss of control is impending, any or all of these measures may be automatically applied to help restore directional stability. It's almost as if the car has a sixth sense.

In fact, in every sense the Outback VDC is a remarkable vehicle. With tactile luxuries like a leather-trimmed, 8-way power driver's seat. A mahogany and leather steering wheel by Momo®. And a state-of-the-art 200-watt* sound system built exclusively for Subaru by McIntosh®. Working together, McIntosh and Subaru engineers placed 11 speakers in 7 strategic locations so the audio quality would be specifically tuned to the car's unique acoustics.

The Outback VDC from Subaru. It is truly a phenomenon in the world of automotive engineering. And we have a feeling you're going to love it. To find out more, come visit us at **www.subaru.com**.

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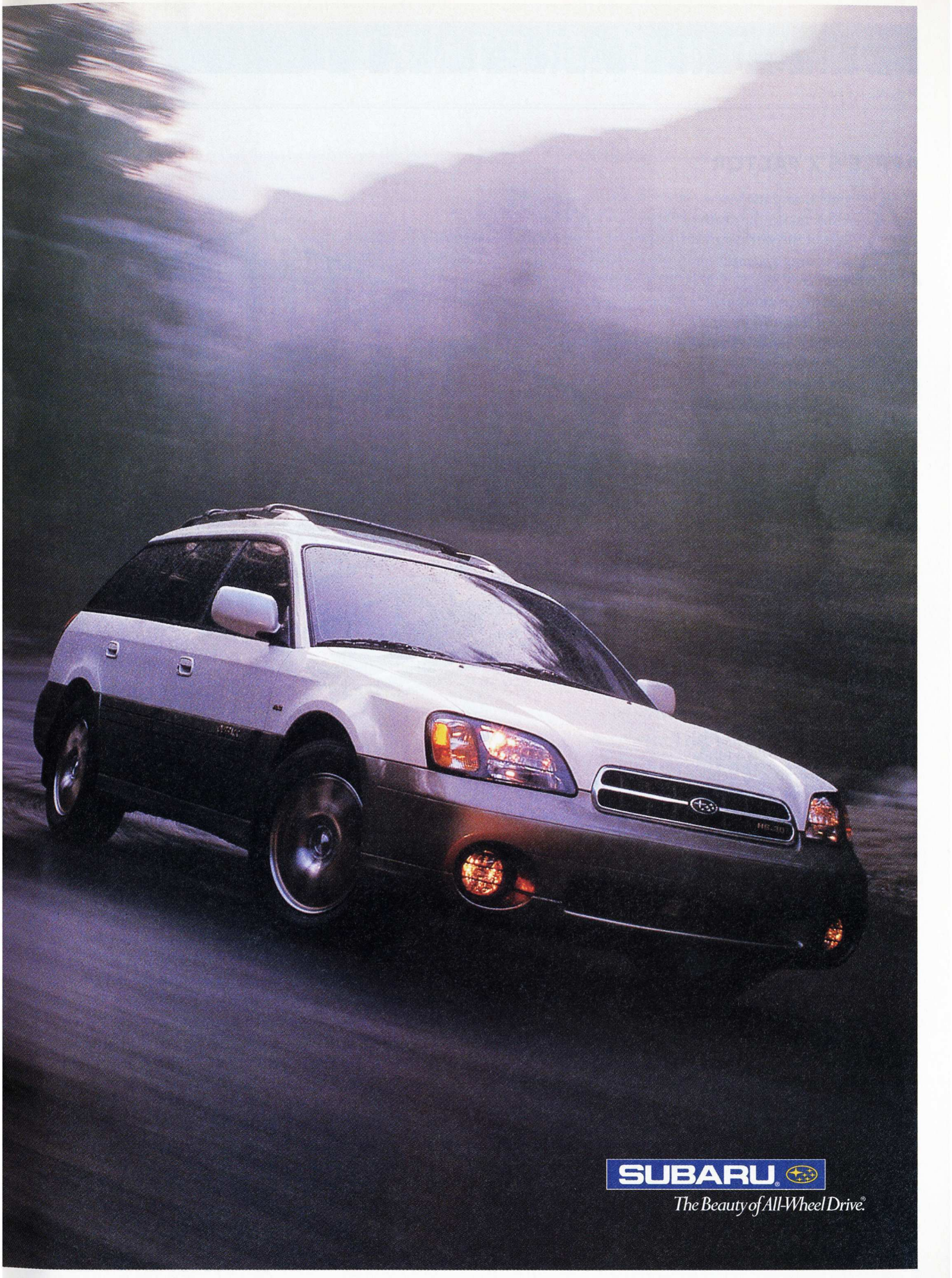
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APPLE'S X FACTOR

NICK DEWAR

Apple Computer's new OS X marks the death of one of the world's great operating systems. Rejoice!

I write this not as an Apple-basher, but as a long-disappointed Macintosh fanatic. Since its birth, the Macintosh has always had an excellent user interface but a crummy underlying operating system. Those problems date back to 1984, when Apple shipped the first Macintosh with Motorola's 68000 microprocessor rather than waiting for the more able-bodied 68010. That choice prevented Apple from incorporating technologies like memory protection and preemptive multitasking into the original Mac. The legacy of that mistake was nearly two decades of system crashes. But all of this history is about to be rendered moot.

With OS X, Apple is making a dramatic departure from the past. OS X (the X means 10) is a fundamentally new operating system that is merely pretending to be a Macintosh of old. This is big news—and not just for Apple users. Indeed, it may be bigger news to people using Microsoft Windows. What makes MacOS and Windows so important is their reach. MacOS is used by tens of millions of people every day, Windows by more than 100 million. These operating systems intimately influence the way people work and think. Their capabilities and limitations set the ground rules of what is possible and profitable for hundreds of thousands of companies. Killing one of these operating systems and replacing it with another cannot help but have far-reaching impacts.

And make no mistake about it—OS X is a different animal. Its visual similarity to earlier Mac systems is only a veneer. Apple's previous operating systems were purebreds, with an unbroken lineage going all the way back to the first Macintosh. OS X is a mongrel. Its foundation is Unix, the operating system that traces its ancestry back to Bell Labs and the late 1960s. And the user interface that sits atop this operating system also comes from outside of Apple; it was developed at NeXT Computers (the company that Steve Jobs started after being kicked out of Apple). OS X can run most existing Macintosh software, but this is done with a kind of computational sleight-of-hand.

Apple is betting that OS X will freshen the MacOS bloodline, overcome the Mac's inbred disorders and provide a new base for future expansion. It's a big gamble. If Apple succeeds, the impact will extend far beyond the current world of Mac users. For starters, OS X could dramatically expand Apple's current user base. More importantly, Apple's increasing relevance will ensure that its innovations will show up in software from Microsoft and in hardware from top PC vendors like Compaq Computer, Dell Computer and Gateway.

To understand the predicament that Apple is trying to dig itself out of—and to understand why a successful turnaround could have such widespread impact—it helps to look at the company's history. As we shall see, the endless comparisons between Apple's MacOS and Microsoft's Windows are misleading at best and, for Macintosh supporters at least, grossly unfair. Apple likes to remind the world that "Apple ignited the personal-computer revolution" when it introduced the Apple II in 1977. In fact, Apple was just one of more than a dozen companies that launched home computers (or "microcomputers," as people called them back then) in the late 1970s.

Each of these computers came with its own operating system: applications software developed for one computer wouldn't run on another. By adopting this strategy, microcomputer makers were following the lead of companies that produced minicomputers and mainframes—companies like IBM, Digital Equipment and Wang Laboratories.

Within a few years of the Apple II's debut, there followed a whole set of "business-class" microcomputers from other manufacturers. Most of these machines ran a common operating system, called CP/M, which had been developed by Digital Research. CP/M was extraordinarily simple—all it could do was read keystrokes, display characters on the screen, manage files on a floppy disk, load programs into memory, and run them.

Rudimentary though it was, CP/M had enough power to give birth to the microcomputer software industry. My first exposure to a computer was with a Xerox-built CP/M machine that my father bought in 1980. It ran dBase II (a database program) and WordStar. When IBM brought out its PC in 1981, it was a late entrant into the game. The company hired a tiny company called Microsoft to write a clone of CP/M called PC DOS. (Microsoft had actually bought DOS from Seattle Computer Products for $50,000 and sold the program as its own.) Like CP/M, PC DOS could do little other than manage disk files, load programs into memory and keep them running.

At the time, Apple was criticized for not building its own CP/M or DOS-based computer. But Apple's business model—and its corporate structure—were based on using proprietary but innovative software so that it could enjoy significantly higher margins on its hardware than its competitors could ever justify. (How IBM overcame its corporate culture to build a PC without its own proprietary operating system is a story that has been well chronicled by others.) So rather than join the pack, Apple decided to leapfrog. Instead of using Intel's popular 16-bit processor, Apple opted for Motorola's new 32-bit 68000. Apple also concentrated on developing a graphical user interface that would make the computer dramatically easier to manage—and thus expand the market to a whole new class of customers who felt put off by the PC's techie look and feel. After two failed attempts (the $10,000 Lisa and the Edsel-like Apple III), the company finally got it right in 1984 when it introduced the Macintosh.

For this reason, attempts to compare Apple to Microsoft misunderstand what drives the two companies. Microsoft innovates software. But with the exception of the Macintosh user interface, virtually all of Apple's innovations have been in hardware. Apple popularized the mouse and 3.5-inch floppy disks. Apple introduced trackballs and then touch pads on laptops—in the process pushing the keyboard to the back of the laptop and creating a wrist rest, which is today standard on almost all portables. Now, Apple is pushing wide-format displays—screens considerably wider than they are tall, more akin to a movie screen than a TV—into the mainstream. Within three years, such displays will probably be standard in the PC world as well.

What's exciting for me about OS X is that this the first time in more than a decade that Apple has introduced a significant software innovation. And oh my, is OS X significant! For starters, consider its geeky underpinnings. For more than three years, analysts have been hailing the arrival of a Unix variant called Linux (or GNU/Linux, to give proper credit to its many developers). But although Linux has charmed the code-breathing set, it has made little headway into homes and businesses because it is too hard to use and too unlike Windows and the MacOS. OS X will change this. Unless an atomic bomb goes off at Apple's headquarters in Silicon Valley, by this time next year Apple will be the world's largest supplier of Unix-based operating systems. OS X will prove that it is possible to give Unix a friendly wrapping. The impact will also be felt by Bill Gates's little enterprise because, for the first time ever, Apple's operating system will be more stable and faster than Microsoft's.

OS X also brings with it Cocoa—a new set of tools for writing desktop applications. These tools evolved from

For the first time in more than a decade, Apple has introduced a significant software innovation. The company is betting that OS X will overcome the Macintosh's inbred disorders.

NeXTStep, the development framework for the NeXT computer. I wrote a book about NeXTStep back in 1993, so perhaps I'm biased. But practically all the programmers I knew told me they could write applications with NeXTStep five to 10 times faster than they could for Windows. If Cocoa is even half as good as NeXTStep (and initial indications are that it is better), we could see an explosion of high-quality applications written by individuals or extremely small companies. This means that OS X has the power to revolutionize the software industry.

Initial reception of OS X has been lukewarm at best. Many users seem to think that Apple invested too many resources in "eye candy." As you move windows around the screen, for example, they stretch and warp as if painted on sheets of rubber. And because OS X is a fundamentally new operating system, it doesn't yet work with many scanners, digital cameras and other peripherals (compatibility will come when the necessary drivers are written). But within a year, these minor problems will have been overcome. What remains will be the start of the next big thing in desktop computing. TR

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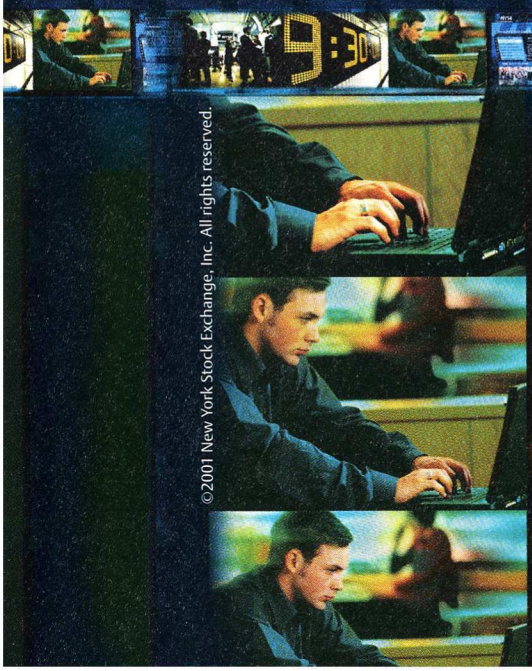

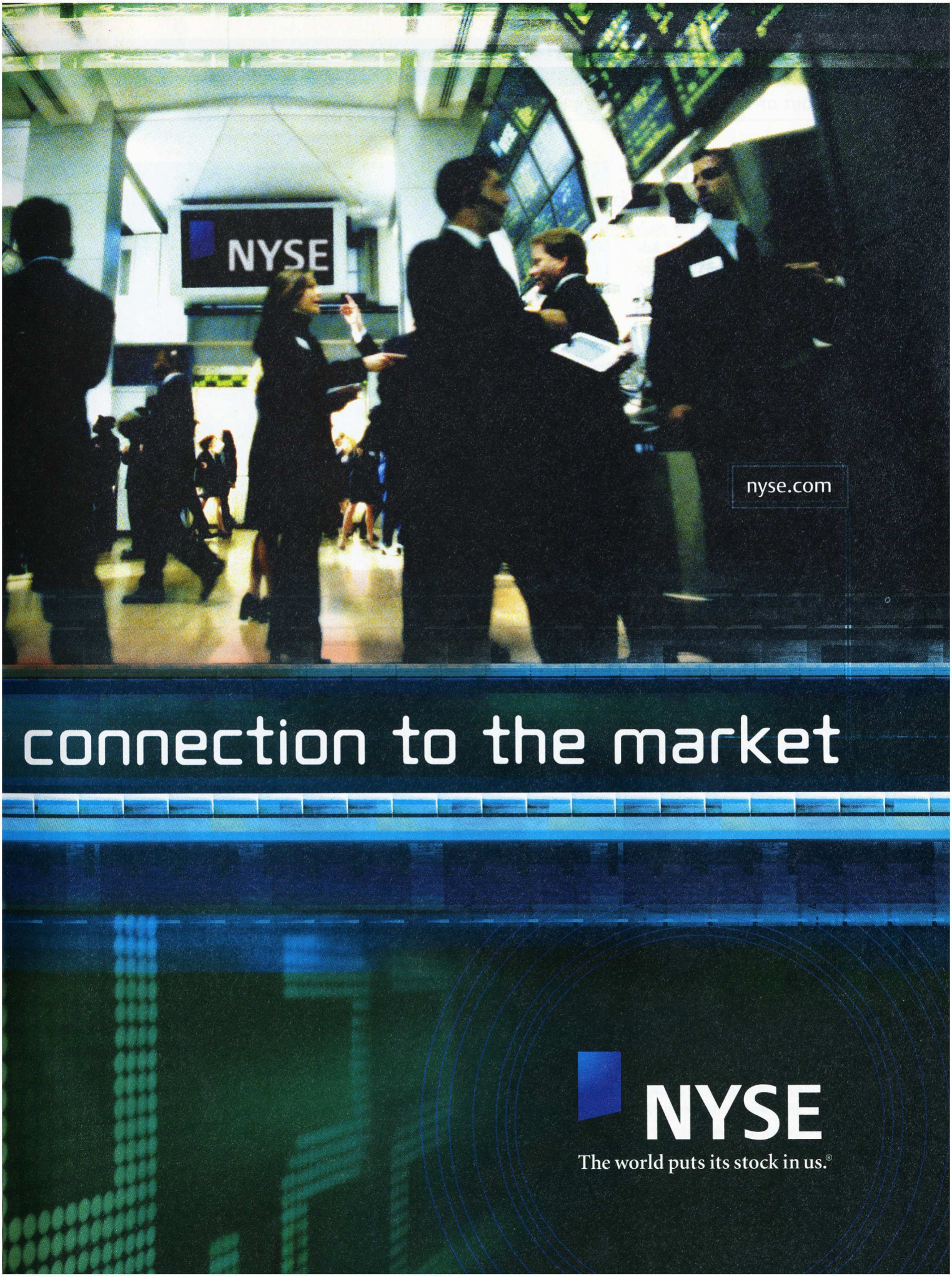
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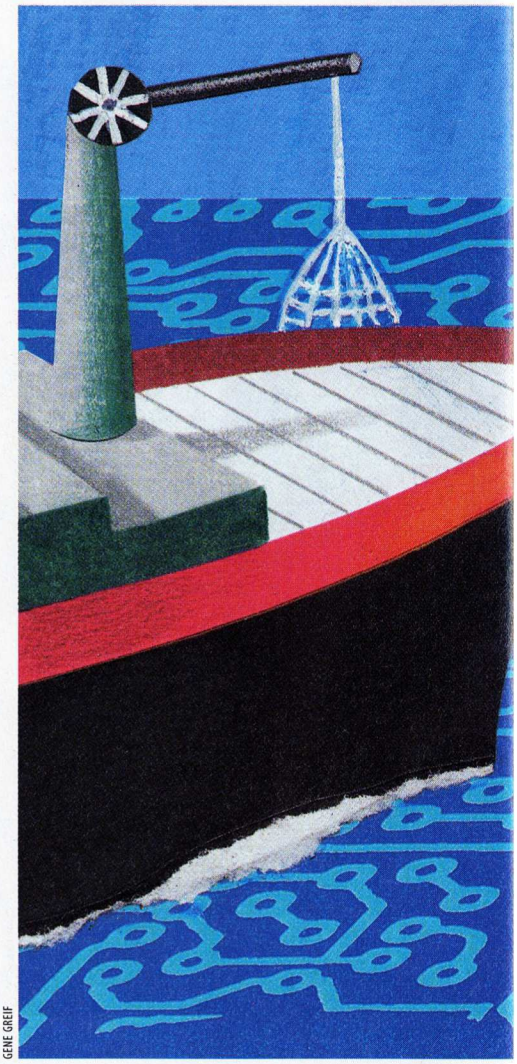
INTEL REVAMPS R&D

A shift in strategy could help broaden the firm's horizons


GENE GREIF

Bring up the U.S. Defense Advanced Research Projects Agency (DARPA) in technology circles, and most people will think of the blue-sky research that the agency funds, like the work that spawned the Internet *(see "DARPA's Disruptive Technologies," p. 42)*. Bring up Intel, and a different image comes to mind: a not very imaginative research-and-development program that cranks out one Pentium processor after another. Great stuff, but hardly research capable of producing tomorrow's technological breakthroughs.

That could all change, as Intel's research director David Tennenhouse is engineering a sweeping overhaul of his organization, modeled largely on DARPA. Tennenhouse, who directed DARPA's Information Technology Office for three years before joining Intel in late 1999, says the problem is straightforward: although Intel will shell out more than $4 billion this year for R&D—ranking it among industry's top spenders—the company rarely ventures off the familiar semiconductor road map into emerging areas like ubiquitous computing, wireless networking and biological computing. But such "disruptive research," Tennenhouse says, is "the research that's going to lead to new business for Intel or open up areas that are going to jar the road map."

Tennenhouse bills Intel's new research structure as a DARPA-like "virtual laboratory." The company will follow the agency's lead by using a small cadre of program managers to identify and fund projects—inside the company and out—that fit Intel's long-term strategy but are beyond the scope of its existing business lines and research. At the same time, Tennenhouse plans to open six to eight small "lablets" near top universities; the first three will be running by this fall.

Intel's modeling of a significant portion of its research—which might eventually total more than $100 million per year—after a government agency appears unique in business, says Harvard Business School's Henry Chesbrough, an expert on industrial R&D. The changes, he notes, illustrate the need for companies to balance the pressure to improve existing products with the desire to hit a few home runs. "Every company has to learn how to access the wealth of ideas that are distributed outside its own four walls," as well as those inside, says Chesbrough.

Tennenhouse spent more than a year studying Intel's R&D structure before he began implementing the new plan last February. The company employs about 6,000 R&D people, almost all in business-division labs. Intel also sponsors some 360 university projects, including several disruptive studies. Tennenhouse didn't want to upset these efforts; he wanted to enhance them and, especially in the case of the disruptive projects, make them part of a more formal long-term strategy. What he didn't want to do was create a separate central research lab like those at IBM, say, or Microsoft.

The answer was to create a small group—fewer than 20 people—to evaluate, fund and oversee the additional disruptive studies he felt would be vital to long-term growth. These efforts can take place in Intel's existing labs or in universities and nonprofit research organizations, in close conjunction with Intel scientists. If and when they mature, the efforts will be brought into the main R&D pipeline.

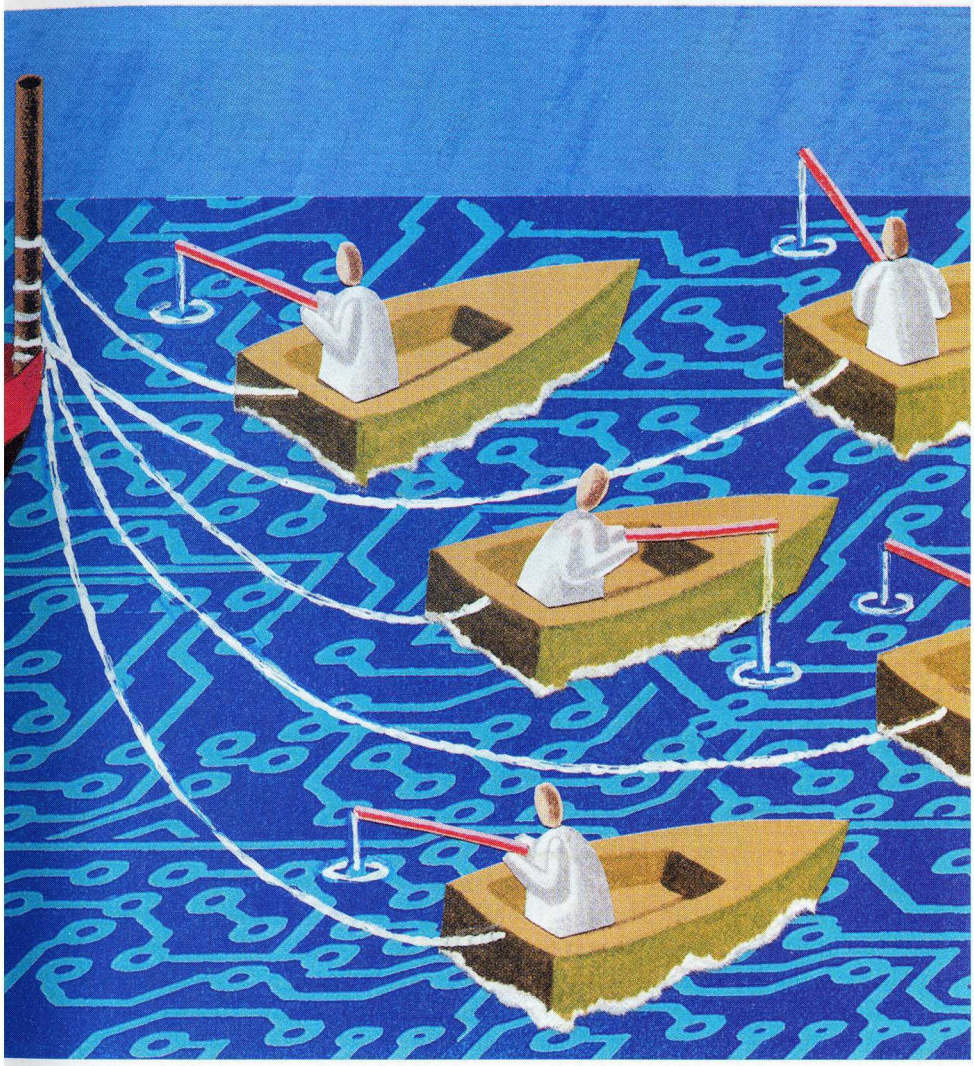
Tennenhouse identified five "sectors" for Intel to explore: microelectromechanical systems (MEMS), distributed systems, biotechnology, statistics and machine vision. Sector directors were charged with developing strategic plans in their areas and working with researchers to develop projects that fit those plans. Projects that make it through an approval process led by Tennenhouse will receive $2 million to $3 million a year for two to four years. In contrast to the vast scale of Intel's conventional semiconductor research, which can involve hundreds of people on a single effort, the ideal disruptive-project size is probably five or six people, says Tennenhouse. "Most good research gets done at that size."

Another principle guiding Tennenhouse's vision is that some of the sponsored projects originate at Intel. Big firms

BRANCHING OUT

Intel's first three "lablets," opening this year

SITE/AFFILIATION	PROJECT
Berkeley, CA/ UC Berkeley	Extremely networked systems, like highway sensor networks
Seattle, WA/ University of Washington	Ubiquitous computing; wireless systems; high-frequency communication
Pittsburgh, PA/ Carnegie Mellon	Software for widely-distributed-storage systems



jects in universities. But Tennenhouse is worried that the focus of university computer science researchers has become too short term—so he hopes the new lablets will become a vehicle for encouraging longer-term efforts. "We really do want them [looking] farther ahead," he says.

Each lablet, which will house 20 to 30 researchers, will help Intel link up with a professor whose work fits with the firm's strategic plans. The researcher will take a leave of absence, maybe two years, to get the lab started. "It's not unusual for companies to establish research labs adjacent to major universities," says Ed Lazowska, chair of the department of computer science and engineering at the University of Washington, near where the first lablet started this July. "What's special, though, is that intimate collaboration with the neighboring university. We're going to have several dozen new researchers located adjacent to our campus, whose mission is to collaborate with us."

A lot of *if*s surround Intel's new structure. Can the lablets, for instance, build enough critical mass to stand on their own in a large organization? And at Intel, admits Tennenhouse, the idea of starting disruptive research in business-unit labs has met with resistance, because it means taking top researchers off vital road map work—or possibly diluting the company's focus on its core business. Tennenhouse figures it will take at least five years to determine if the new model is working—and probably more. And then, even if some great projects make it "downstream" into the main R&D fold, he'll have another worry: "The problem is, [if] the really good or great people take their projects downstream, that can leave you with people that are pretty good but not great." That, he says, would be a sure way for the new effort to wither. —*Robert Buderi*

Although Intel will shell out more than $4 billion this year for R&D, the company rarely ventures off the familiar semiconductor road map into emerging areas.

tend to expect disruptive ideas to come from outside the box—and outside their walls. Tennenhouse, though, thinks the opportunity to work on disruptive projects will be a creative spark for current employees—and could even become a great recruiting and retention tool.

Many of the initial efforts funded, in fact, are taking place in-house. One is Roy Want's "Ubiquity" project. The idea is that in the future people will carry "personal servers" through which they issue commands or make requests. But rather than harbor displays and do all the computing themselves, the devices will tap into local computing infrastructure. Say you want to review a PowerPoint presentation while on the road, Want says. Your device would relay the request wirelessly to the local network, and the page would be shown on the nearest display—a hotel-room television or office monitor. Before Intel, Want was at Xerox's Palo Alto Research Center, which supports many such disruptive projects. But he says the Intel program is unlike anything at PARC in that his work is now done in close association with a business unit. At PARC, he says, far-out efforts "ran free," with no connection to Xerox businesses.

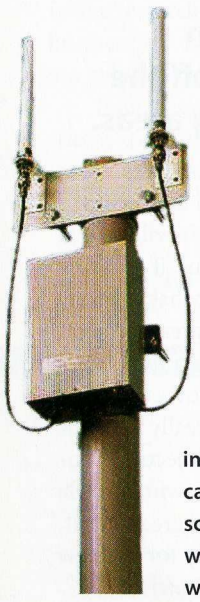
In parallel with in-house efforts, Intel will step up its funding of disruptive pro-

CALLING ALL VILLAGES

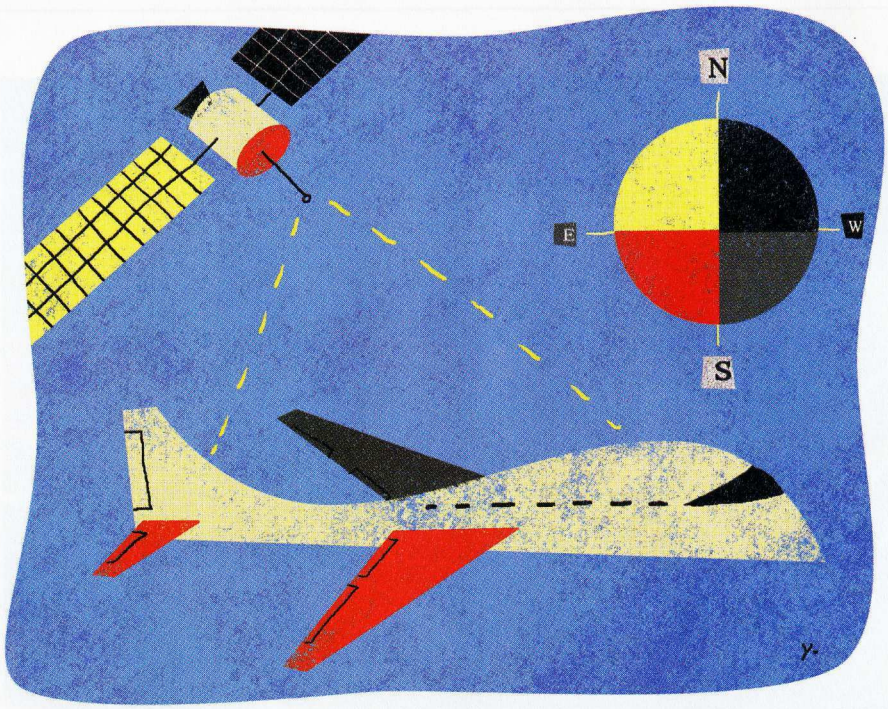
TELECOM | For many people in rural areas of the developing world, just making a phone call from home is a distant dream. That's because building conventional phone infrastructure costs around $1,000 per home; to break even, companies would have to charge an amount out of reach for most would-be customers. But a new wireless telecommunications technology called corDECT could change that, potentially bringing millions of people not only phone access but the Internet as well.

Developed jointly by the Indian Institute of Technology in Madras and Midas Communication Technologies in Chennai, India, the new system is cheap and easy to install, as it replaces expensive cabling with wireless base stations *(below)*, each serving 30 to 100 subscribers in a neighborhood. An answering-machine-sized box in each user's home has ports for a phone and a computer. The system allows the phone and computer to share bandwidth: if a call comes in while somebody is surfing the Web, the Internet connection speed simply slows. The cost: $200 per home.

That price tag has prompted widespread interest in corDECT and pilot implementations of the technology in 11 countries, including Madagascar, Fiji, Kenya, Brazil and India. Harvard University's Center for International Development, together with the MIT Media Lab's Digital Nations consortium, chose corDECT for its project to connect communities in southeastern India. Says Colin Maclay, deputy director of the Harvard center, "We went with corDECT because it was cheap, robust and could scale up easily to a thousand villages." For the more than 95 percent of India's billion inhabitants who currently can't afford a phone, that scalability could mean a whole new connection to the world. —*Venkatesh Hariharan*



COURTESY OF MIDAS COMMUNICATION TECHNOLOGIES



JAMES YANG

GPS CLEARED FOR TAKEOFF

More accurate data could soon help guide planes

TRANSPORTATION | In a bid to modernize the U.S. air traffic control system and avert air travel gridlock, the Federal Aviation Administration has formulated a 10-year, $11.5 billion plan to replace today's radar-based system with one built around satellites. The project relies largely on Global Positioning System data, rather than radar, for navigation. The problem is that GPS still isn't accurate or reliable enough for such aviation applications. Now, a system that would allow GPS to provide nearly infallible signals for air traffic use is getting ready for rollout. If the technology passes testing over the next several years, it could help make the FAA's grand vision a reality.

In the new system, 25 ground stations constantly check the accuracy of the GPS signal. Software corrects glitches caused by things like atmospheric disturbances, and the stations beam corrected information to pilots via a pair of satellites. After seven years of trying, Raytheon of Lexington, MA, is expected to deliver the system as early as March 2003, the FAA says. "Everything is really coming to a head," says Timothy Katanik, a Raytheon manager working on the system. "We think we are there now."

Satellite-based air traffic control promises greater flexibility and capacity than radar-based systems *(see "The Digital Sky," TR March 2001)*. Pilots could freely optimize their routes and not herd themselves into clogged "highways" set by radar beacons. And when landing in bad weather, pilots could use satellite data to follow a variety of approach patterns, instead of the single rigid path required by runway landing signals. All this could mean shorter trips and fewer delays.

Refinement of GPS signals won't come cheap, though. And additional ground stations based near each airport will be needed for, say, landings in zero visibility. The total cost could run as high as $4.6 billion, says Hal Bell, the FAA's product leader on the system. And don't expect fewer delays at LaGuardia anytime soon. GPS will initially just help pilots land at remote airports that currently lack radar; FAA approvals for large, busy airports, and for zero-visibility landings and other tough situations, could take up to 20 years, Bell says. Which means passengers could be waiting for improved on-time rates for quite a while. —*David Talbot*

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$155,250,000 Tellium Initial Public Offering May 2001 Co-manager	$228,000,000 burleigh has been acquired by EXFO December 2000 Sole advisor to Burleigh	$49,500,000 AFOP Initial Public Offering November 2000 Co-manager	$2,458,125,000 CORNING Follow-on Offering November 2000 Co-manager	$132,825,000 OCP Initial Public Offering November 2000 Co-manager	$1,050,000,000 photonetics has been acquired by GN Nettest November 2000 Sole advisor to Photonetics
ASTARTE FIBER NETWORKS INC has been acquired by Tellium, Inc. September 2000 Sole advisor to Astarté	$673,223,000 BOOKHAM technology Follow-on Offering September 2000 Co-manager	$358,400,000 Newport. Follow-on Offering July 2000 Co-manager	$209,300,000 EXFO Initial Public Offering June 2000 Co-manager	$1,800,000,000 PIRI® has been acquired by SDL, Inc. June 2000 Sole advisor to PIRI	$150,000,000 NZ Applied Technologies has been acquired by Corning Inc. May 2000 Sole advisor to NZ Applied Technologies
Optigain, Inc. has sold a controlling interest to FITEL Technologies, Inc. May 2000 Sole advisor to Optigain, Inc.	$2,950,000,000 ORTEL CORPORATION has been acquired by Lucent Technologies April 2000 Sole advisor to Ortel	$352,439,000 BOOKHAM technology Initial Public Offering April 2000 Co-manager	$28,125,000 itf OPTICAL TECHNOLOGIES Private Placement April 2000 Sole agent	$772,500,000 Finisar Follow-on Offering April 2000 Co-manager	$15,000,000 BOOKHAM technology Private Placement February 2000 Sole agent
$2,263,056,000 CORNING Follow-on Offering January 2000 Co-manager	$176,795,000 Finisar Initial Public Offering November 1999 Co-manager	$525,000,000 JDS Uniphase Public Placement November 1999 Sole Agent	$400,000,000 EPITAXX has been acquired by JDS Uniphase November 1999 Sole advisor to Epitaxx	$278,185,000 SDL Follow-on Offering September 1999 Co-manager	AFC AFC TECHNOLOGIES INC. has been acquired by JDS Uniphase August 1999 Sole advisor to AFC
$265,650,000 E-TEK DYNAMICS Follow-on Offering August 1999 Co-manager	$878,923,000 JDS Uniphase Follow-on Offering July 1999 Co-manager	$6,800,000,000 uniphase has merged with JDS FITEL July 1999 Advisor to Uniphase	$113,190,000 OCLI Follow-on Offering May 1999 Co-manager	$84,700,000 Harmonic Follow-on Offering April 1999 Co-manager	uniphase has acquired Philips Optoelectronics B.V. June 1998 Sole advisor to Uniphase

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ELECTRONIC MEDICAL RECORDS

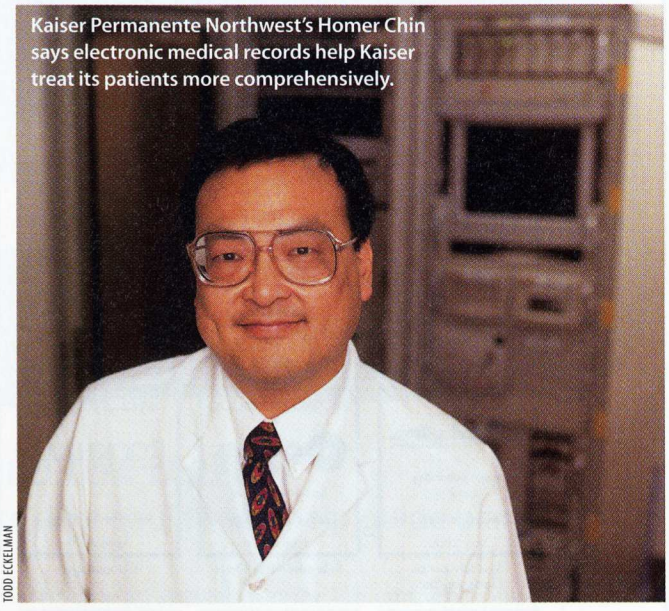
New rules mean doctors must go digital

MEDICINE | Doctors hear it all the time: if they kept patients' files on computers instead of on paper, it would save time and money—and patients would get better care. Still, less than five percent of U.S. physicians use electronic record systems. But new regulations from the U.S. Department of Health and Human Services could finally force doctors to enter the digital age.

None of the regulations, the first set of which is due to take effect in October 2002, prohibits the use of paper records, but they require health-care organizations to document and manage so much information that paper-based offices will likely find themselves unable to comply. "The whole field of medicine is going to change dramatically," says David Kibbe, CEO of Canopy Systems, a clinical software firm in Chapel Hill, NC.

The regulations, combined with rising concerns about medical errors, have prompted nearly two-thirds of doctors to make plans to implement electronic record systems, according to a recent survey by the research firm Gartner. And some 300 software companies nationwide are waiting in the wings, offering everything from speech recognition software to replace note-taking to programs that help doctors make treatment decisions.

The medical offices of Oregon managed-care giant Kaiser Permanente Northwest went electronic in 1994, converting all their lab tests, notes and treatment guidelines to digital files. According to Kaiser physician Homer Chin, the company has saved $5 million a year in labor costs alone. Still, about 70 percent of doctors work in small practices that probably won't be able to invest millions of dollars in their own computer systems and may instead turn to outside vendors to store and manage their records over the Internet. "The market for these vendors is huge," says Thomas Handler, a health-care analyst at Gartner. And the potential for more effective, and safer, health care could be even greater. *—Alexandra Stikeman*



Kaiser Permanente Northwest's Homer Chin says electronic medical records help Kaiser treat its patients more comprehensively.

TODD ECKELMAN

DIGITAL PRESERVATION

SOFTWARE | **Increasingly, the record of our civilization is becoming digital, from census data to family photos. The Library of Congress alone has 35 terabytes of files. Yet rapid changes in computers and software could render this data unreadable.**

Congress recently allocated the library $100 million to look for a way to preserve its files—one of the most ambitious efforts yet to tackle digital obsolescence. "With that money we'll be able to gather the technical people and the archivists and start to develop a prototype," says Abby Smith, preservation program officer with the Council on Library and Information Resources, which is working on the project.

Part of the challenge is that computers and software gallop ahead, while digital files remain static. The library's current solution is to convert files to work with the updated systems every few years, but "every time you convert something, you change it," says Jeff Rothenberg, researcher at the Rand Corporation in Santa Monica, CA. Rothenberg instead sees a solution in emulation software that can mimic a given hardware platform, allowing one computer to act like an earlier one. To demonstrate the approach's feasibility, he created a chain of emulators linking a present-day PC to the 1949 EDSAC, one of the first computers. "I was able to run any of the original EDSAC programs that were saved on paper tape," he says.

Ray Lorie, research fellow at IBM's Almaden Research Center in San Jose, CA, is working on an approach that creates a digital road map of a document at the time of its creation. Write a document, say, in Adobe Premier, and the software generates a second file that describes the content and formatting of the original document using a simple code. That code would be readable by a "universal virtual computer"—an emulator that mimics, not an earlier machine, but a hypothetical, extremely simple computer. "In the future we'd only need some way of interpreting this single virtual computer," says Lorie.

AP PHOTO ARCHIVE

Will the data on these tapes soon be illegible?

While the Library of Congress appropriation won't solve the problem of digital preservation, it will allow for the first large-scale testing of possible solutions like Lorie's and Rothenberg's. "The Library of Congress project has a high enough profile that we might be able to get the attention of technology industry, and to finally get some answers," says Smith.
—Claire Tristram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PERSONAL GENOMES

Individual sequencing could be around the corner

BIOTECH | The Human Genome Project's working draft sequence, which was completed to much fanfare in June 2000, took about a dozen years and more than $300 million to complete. The result was a composite map of the DNA from several people—a sort of averaged genetic picture of a human. But a growing number of companies are working on advanced technologies that could make it possible to have your own individual genome sequenced in a day, perhaps for as little as a few thousand dollars.

No one's genetic makeup matches "the human genome" exactly; the differences are what give one person brown eyes and another blue or make some people more susceptible to heart disease. The new technologies could give anyone access to the unique, letter-by-letter sequence of his or her entire genome and help doctors detect the variations that signal health problems down the road.

Today's sequencing methods are costly and slow in part because for each DNA letter read—of the roughly three billion in a human genome—researchers need to synthesize a separate copy of the DNA strand. Making the copies requires several chemical reactions; then you have to separate and identify the newly made strands. In contrast, two new techniques being developed could read the sequence directly from one DNA molecule. The first method, called "nanopore sequencing," involves pushing a strand of DNA through a tiny hole surrounded by sensors that detect the electrical changes caused by each DNA letter. The second takes advantage of an enzyme called DNA polymerase, which copies DNA inside our cells. Researchers use specialized optics to detect each letter added as the enzyme copies the original DNA strand.

In May, Palo Alto, CA-based Agilent Technologies signed an agreement with Harvard researchers Daniel Branton and Jene Golovchenko to further develop nanopore sequencing, which Branton coinvented *(see "Hole in the Wall Offers Cheaper Sequencing," TR May/June 1998)*. Also this year, Woburn, MA-based U.S. Genomics received its first patents on technologies that combine the two direct techniques. Thanks to these and several other efforts *(see table)*, the dream of sequencing a human genome in just a day could be a reality in two to five years, says George Weinstock, co-director of the Baylor College of Medicine Human Genome Sequencing Center in Houston. "They're all very clever techniques," he says. "We're getting very close to having them in hand."

Though the new sequencing tools will initially be used for biomedical research, they could eventually find their way into doctors' offices, not only providing for quick gene-based diagnosis of a host of diseases, but also helping doctors choose medicines tailored to individual patients. The expected price tag to sequence your genome—perhaps $5,000 to $30,000—might seem steep, but "it's kind of a life investment," says Harvard Medical School biophysicist George Church. "I would pay $10,000 to get my genome sequenced...rather than buying a second car." —*Erika Jonietz*

SEQUENCE SEEKERS

Others pursuing single-genome techniques

NANOPORE	POLYMERASE
Amersham Pharmacia Biotech (Piscataway, NJ)	LI-COR Biosciences (Lincoln, NE)
Eagle Research (Broomfield, CO)	Solexa (Little Chesterford, England)
EIC Laboratories (Norwood, MA)	

BUILDING A GREEN FUTURE

ENERGY | Picture that monthly envelope from the electric company and imagine that it contains not a bill but a statement of credit—every month. That's the future of homes and other buildings, as seen by the U.S. Department of Energy. The agency hopes that its new road map for building-technology research and development will help make this green vision a reality by 2020.

Developed in conjunction with the building industry, the road map sets goals for improving building "envelopes"—walls, windows, foundations and roofs. According to Mark Ginsberg, the agency's deputy assistant secretary in the Office of Building Technology, shortcomings or defects in a building's envelope can be responsible for as much as half of its energy consumption: poor insulation wastes heat, for example, and air leaks make air conditioners work overtime. The department's funding of research for the next two decades, Ginsberg says, is meant to produce "the next generation of insulation, roofing materials and building products that will perform significantly better than what we have today."

JAMES YANG

Instead of replacing a roof, for example, you might someday be able to simply spray a plastic foam over the existing shingles that provides not only waterproofing but also an additional layer of insulation. Intelligent lighting and climate control systems could learn your preferences and adjust each room to suit your needs as you move through your home—making the most efficient use of heating, cooling and electricity. And solar cells integrated into not only roofs, but exterior walls as well, could help a building generate its own power.

"My own personal goal," Ginsberg says, "is 120 percent energy efficiency—buildings that use so little energy, and produce their own, that they give back to the grid." And, come bill time, they'd give back to their owners as well. —*Lauren Gravitz*

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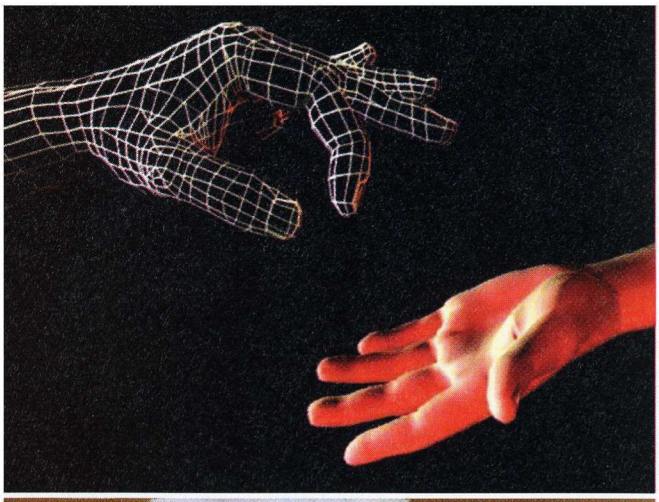

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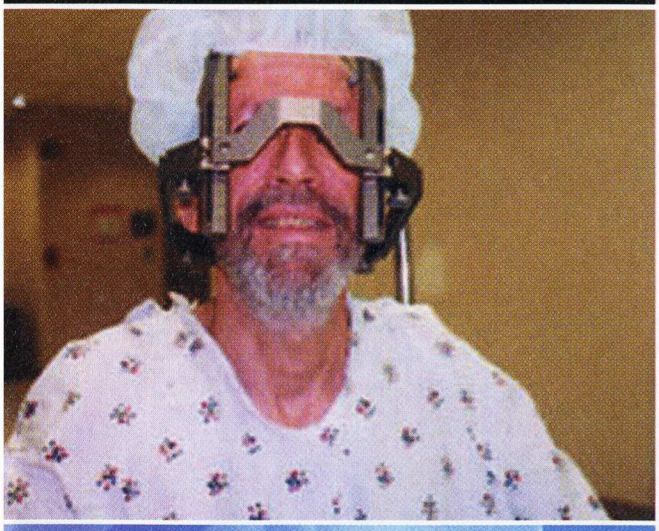

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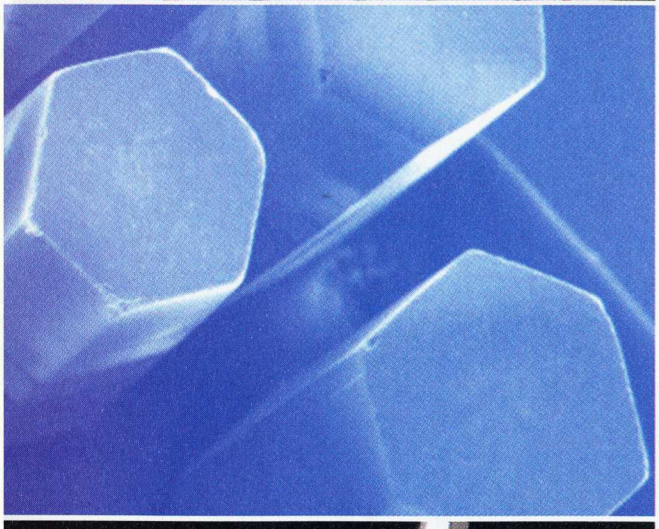

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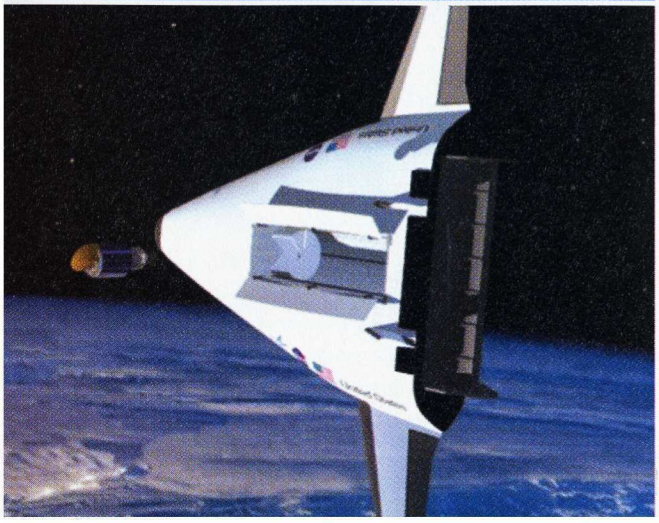

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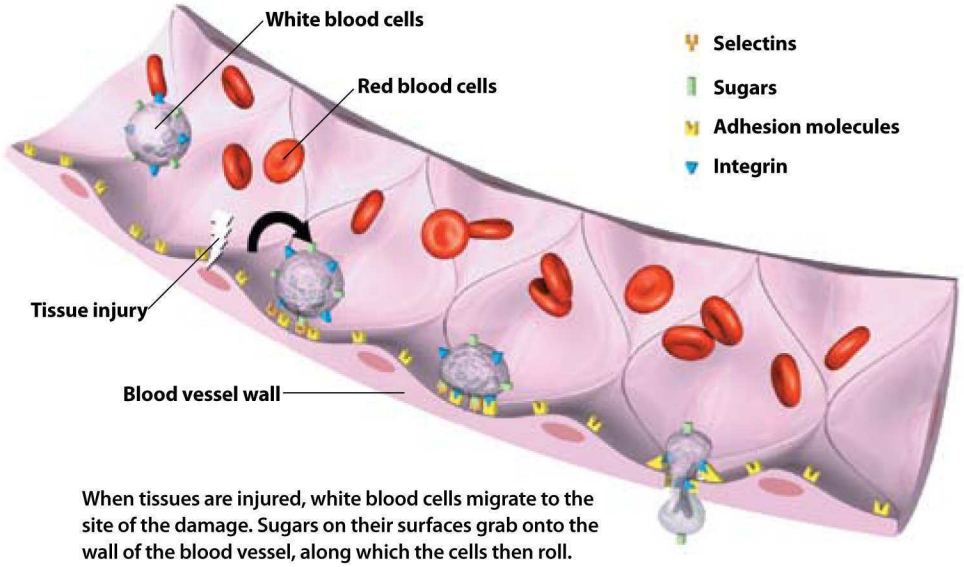

When tissues are injured, white blood cells migrate to the site of the damage. Sugars on their surfaces grab onto the wall of the blood vessel, along which the cells then roll. The white blood cells ultimately squeeze between the cells making up the blood vessel and address the injury.

JOHN MACNEILL

GLYCOMICS

Sugars could be biology's next sweet spot.

The 1990s may well be remembered in biology as the decade of the gene, culminating in the completion of the Human Genome Project's working draft. And the next big thing in medicine may be the study of the proteins coded for by all those genes *(see "The Proteomics Payoff," p. 54)*. But even as doctors and drug companies struggle to interpret and exploit the recent explosion of data on genes and proteins, yet another field of biology is waiting to break out: glycomics. This emerging discipline seeks to do for sugars and carbohydrates what genomics and proteomics have done for genes and proteins—move them into the mainstream of biomedical research and drug discovery.

For years, carbohydrates were one of the least glamorous subjects in biochemistry research. At best, scientists thought, these molecules created structure (in the cell walls of plants, for example) or were used to store energy (think potato); at worst, they hindered the study of important biological molecules like DNA and proteins. However, a very different portrait of sugars is gradually emerging. Biologists are finding that minor differences in sugar structures can have a huge impact on biological functions; in fact, sugars are involved in everything from embryonic development to regulation of the immune system. "Sugars are everywhere, in all organisms," says David Zopf, a vice president at Horsham, PA-based Neose Technologies, one of a number of research groups and companies working to exploit glycomics.

The commercial buzz is being created by the realization that a better understanding of sugar biology could ultimately lead to new drugs, new targets for conventional drugs and even improvements in the activity of existing drugs. Modifying protein-based drugs with the appropriate sugars, for example, could create far more efficient treatments and reduce the required doses. That's because current methods of making protein-based drugs do not always modify the proteins with the same sugars found on natural versions; this causes the liver to quickly flush the protein therapeutics out of the body. Cancer is another area where sugars turn out to play a big role, helping to transmit the signals that trigger unchecked cell growth; companies are looking to exploit this knowledge to tackle or slow the progress of the disease.

One reason that sugar biology, or glycobiology, has lagged behind the study of genes and proteins is that, until very recently, researchers lacked effective tools for studying carbohydrate molecules. Part of the problem is the complexity of sugars. While DNA and proteins have essentially linear sequences, sugars branch; DNA has just four basic building blocks and proteins have 20, but sugars have more than 30. "We truly haven't cracked the code yet," says MIT glycobiologist Ram Sasisekharan. "We are just beginning to unravel the mysteries of sugars."

Indeed, Sasisekharan's lab developed the first practical method for sequencing sugars only two years ago. And MIT chemist Peter H. Seeberger demonstrated the first automated machine for sugar synthesis in February. Just as the invention of the automated DNA sequencer and synthesizer in the mid-1980s opened up the field of genomics, the availability of such tools is heating up glycomics.

Knowledge of sugars' functions could affect medicine far beyond improving drug doses and fighting cancer. Researchers are looking into how sugars influence the development of Parkinson's, Alzheimer's and infectious diseases like AIDS and herpes, to name a few. Sugars also seem poised to influence stem cell biology, organ transplantation and tissue engineering. If these promising areas of research prove successful, "sugar pills" will take on a whole new meaning. —*Erika Jonietz*

CARBO LOADING

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Glycodata (Ashdod, Israel)	Computer- and biochip-based analysis
Neose Technologies (Horsham, PA)	Sugar-based drugs; protein modification
SafeScience (Boston, MA)	Sugar-based drugs to treat cancer

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CONTENT DISCONTENT

If anything illustrates the tension between the creators and distributors of "content" in our innovation-driven economy, it is the aftermath of June's U.S. Supreme Court decision in *New York Times v. Tasini*—the David-and-Goliath case in which a small and determined band of freelance writers prevailed over a powerful group of well-heeled publishers.

I'll give the particulars in a moment, but what's notable here is that new realities—read the Internet, telecommunications and globalization—have spawned unrest in the fundamentally symbiotic relationship between "content" creators and distributors almost everywhere you look. Screenwriters and actors have been fighting the Hollywood studios. Musicians and record labels have wrangled over Napster. Even the antiglobalization demonstrators in Seattle, Quebec City and Genoa, Italy, underscore the fact that many of today's hottest and most confusing debates hinge on who should control—and profit from—the content that drives an ever growing piece of the world economy.

"Content": in the modern lexicon, the term denotes everything from the information delivered daily to our doors on newsprint to the multimedia clips streamed over the Internet; from the music carried on the airwaves to the interactive software on CD-ROMs. This so-called content is produced by an increasingly broad and diverse segment of the economy, including not just writers and artists, but also software programmers and other high-tech researchers who create new intellectual property.

And here's the most interesting part. Time and again, the distributors—such as publishers, broadcasters and record labels—recoil in the face of technological advances that could diminish their role. As a result, the distributors find themselves blocking developments and standing at odds with content creators. Think of the way the record labels opted to shut down the wildly popular Napster rather than forge a way to take advantage of the new means to distribute music online.

I feel certain that the "new realities" will ultimately favor content creators. After all, content distribution has become easier, more direct and more immediate than ever. Distributors will come out the losers unless they take an enlightened approach to profit sharing with creators in the new media.

If the Tasini case is any indication, however, the transition is likely to be stormy.

The story starts in 1993, when 11 freelance writers, including Jonathan Tasini, president of the National Writers Union, brought a lawsuit charging that publishers—including the parent companies of the *New York Times*, *Newsday* and *Time*—had illegally resold their work to LexisNexis and other databases without the writers' permission. The writers were outraged to find their articles appearing in online databases even though they had never given their permission or received any recompense for the republication of their works.

This spring, the Supreme Court by a seven-to-two margin affirmed the unanimous U.S. Court of Appeals verdict that the publishers had acted unlawfully. The writers, it ruled, should retain the rights to control online republication of their work unless they chose to explicitly sign these rights away by contract. Currently, most standard writers' contracts sell only so-called first-serial rights for an article's one-time use.

But most telling is what happened next. The National Writers Union called upon publishers to negotiate a settlement on how to cut writers more fairly into any profits earned from the online dissemination of their work. Instead, the New York Times Company, for one, opted to fight its freelancers over the matter. Litigious throughout, the publisher announced it would remove the disputed works—some 115,000 articles by 27,000 writers—from distribution online. The *Times* is forcing all current writers to sign away their online rights. And, along with other publishers, *Times* management is lobbying Congress to amend copyright law to retroactively eradicate any financial liability to compensate authors for past copyright violations.

New realities have upset the symbiotic relationship between publishers and content creators. It is time for the New York Times Company et al. to reach an equitable solution with writers.

So now, the writers are forced back into court, this time bringing a class action lawsuit against the Times Company and other publishers to win compensation and to get them to comply with the law. In my view, even if the *Times* and other publishers do yank the articles in question, they have still already profited illegally from the articles' online dissemination and are thus likely to lose the new legal case against them.

Not only do the writers have the law on their side, the National Writers Union has launched a software system that automatically registers copyrighted works and tracks their resale online, receiving payments from participating publishers and paying writers a share of each transaction. All writers can utilize this Publication Rights Clearinghouse. The effort illustrates that the technology for profit sharing is by no means an insurmountable obstacle, as the *Times* might like to claim.

Enough. It is time for the New York Times Company and other large publishers to negotiate an equitable solution that recognizes the extent to which they depend on and profit from the work of independent creators of "content." The central question is: when will they and other content distributors get the message?

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Digital anarchist: Karl Fant of Theseus Logic wants to take chip technology in a radical direction. A small cadre of researchers and companies are coming around to the idea.

it's time for CLOCKLESS CHIPS

A COMPUTER CHIP WITHOUT A CLOCK IS LIKE A…WELL, A MUCH FASTER AND BETTER CHIP. BUT IT'S BEEN A LONG STRUGGLE TO MOVE THESE CONVENTION-BUSTING DESIGNS OUT OF THE LAB.

by claire tristram
photograph by angie wyant

"We're replacing dictatorship with anarchy!" Karl Fant tells me emphatically. Ponytailed and animated, the founder and chief technical officer of Theseus Logic fills the whiteboard with sweeping illustrative examples, kneeling down to use every bit of available writing space. He is in his socks. "Eventually every chip will be designed this way," he declares. "It's inevitable!"

Even in Silicon Valley, where company founders are known to indulge their nonconformist tendencies, Fant's Sunnyvale, CA, office comes as a surprise. His low desk is covered by a formless mass of memos and transcripts and other paper stuff, all mounding slightly toward the middle. There are no chairs—only pillows strewn artlessly about on the floor. If you happen to be me, you begin to regret wearing a dress and wonder where exactly you're meant to sit. But no: Fant leads you to a conventional conference room next door, where, thankfully, there is a chair. That's where he begins to evangelize about the coming revolution intended to wrest computer chips from the constraints of the past.

How? By throwing out the clock, the fundamental way that chips, since the dawn of the Computer Age, have organized and executed their work. Even those of us who know nothing about microprocessors know something about their clocks—Intel for years has used the clock speed of its microprocessors as a marketing tool, where faster is better. The number that dominates most computer ads, along with price, is a label like "1.3 GHz" (or gigahertz). That figure refers to the speed of the clock that governs the internal operation of the machine's microprocessor. Within every one-gigahertz microprocessor, for instance, there lies an oscillating crystal ticking one billion times a second. Engineers are trained to design chips where their first consideration is getting work done before the next clock-tick comes around.

A chip without a clock would be about as useful as a page of text without any space between the letters. For most chip designers, throwing out the clock is difficult to imagine.

But not for Fant or his fellow iconoclasts working on clockless chips at start-ups, universities and corporate labs. It's a small group of ardent believers. Their annual conference attracts only a few hundred participants. Leaders in the field know one another well, and have one another's cell-phone numbers memorized. But while their methods and markets differ, they are united in their belief that clocked chips have run their course, and stand convinced that the advantages of their maverick approach, known alternatively as "asynchronous design" or "self-timed circuits," are so great that the chip industry will ultimately have no choice but to embrace it.

"Designers are realizing that distributing a clock across ever more complicated systems is becoming more and more difficult, and that sooner or later it won't work," says Alain Martin, a professor of computer science at Caltech, who built the first clockless microprocessor in 1989. He points out that as chips get more complex, more and more of the power it takes to run them gets eaten up by the clock itself, which now needs to coordinate the work of millions of transistors.

Dispensing with this overhead confers large advantages on asynchronous chips. One is vastly improved electrical efficiency, which leads directly to prolonged battery life. The clockless technology also yields an edge in computing speed. In labs at Sun Microsystems, Intel and IBM, clockless chips have increased the pace at which high-end processors do their work. In 1997, Intel developed an asynchronous, Pentium-compatible test chip that ran three times as fast, on half the power, as its synchronous equivalent.

At Theseus, Fant has focused on still another benefit of asynchronous design. Because these chips give off no regularly timed signal, the way clocked circuits do, they can perform encryption in a way that is harder to identify and to crack. Improved encryption makes asynchronous circuits an obvious choice for smart cards—the chip-endowed plastic cards beginning to be used for such security-sensitive applications as storage of medical records, electronic funds exchange and personal identification.

Are Fant, Martin and other clockless champions right? Frankly, yes. And yet despite the technology's clear advantages, clockless chips remain more theory than practice. The Intel device, for instance, never made it out of the lab. The failure of clockless chips to gain ground, in fact, makes them a perfect case study of a development with overwhelming promise that nevertheless faces huge obstacles to market introduction—even in an industry known for continuous and rapid innovation.

Like a team of horses that can only run as fast as its slowest member, a clocked chip can run no faster than its most slothful piece of logic. But transistors in a clockless chip can swap information independently, running at the average speed of all components.

The Path Not Taken

The founders of modern computer technology contemplated asynchronous design as early as 1946. But these early computer engineers chose instead to go with a clock. "At the time, it was the right choice," says Jo Ebergen, a senior staff engineer at Sun who works in an asynchronous research group headed by Sun fellow and vice president Ivan Sutherland. (In 1989, Sutherland, best known as a pioneer in computer graphics, wrote a paper that nearly single-handedly reignited interest in clockless-chip technology.) "The circumstances in which they had to design, using vacuum tubes and relay circuits, meant that they really couldn't build a reliable computer without a clock governing the whole thing," he adds. By using a clock, engineers could build in fail-safe measures that made computers reliable even when the parts they were made from weren't.

From that first choice came the steamroller effect of Moore's Law, wherein nearly all research, development and production in the semiconductor industry has focused on clocked chips. By the 1960s, the notion of clockless chips had all but disappeared—kept alive only by an esoteric paper or two coming out of universities. In today's chips, therefore, the clock remains the key part of the action. As a microprocessor performs a given operation, electronic signals travel along microscopic strips of metal—forking, intersecting again, encountering logic gates—until they finally deposit the results of the computation in a temporary memory bank called a register. Let's say you want to multiply 4 by 6. If you could slow down the chip and peek into the register as this calculation was being completed, you might see the value changing many times, say, from 4 to 12 to 8, before finally settling down into the correct answer. That's because the signals transmitted to perform the operation travel along many different paths before arriving at the register; only after all signals have completed their journey is the correct value assured. The role of the clock is to guarantee that the answer will be ready at a given time. The chip is designed so that even the slowest path through the circuit—the path with the longest wires and the most gates—is guaranteed to reach the register within a single clock-tick.

With a central timepiece governing the action, engineers don't have to worry about the varying lengths of millions of infinitesimally small wires; signals can arrive at the register in any order, as long as they all settle in before the clock next ticks. Teams of hundreds of engineers can coordinate their work around the unifying principle of the clock. And we all benefit: the discipline of clock-based design has enabled the magic of exponential growth in chip performance to endure for more than 30 years. "The clock has to go down as one of the most brilliant ideas in design," says Kevin Normoyle, a Distinguished Engineer at Sun who works on the design of Sun's Sparc microprocessors. "It's so simple, and yet it's an approach that has scaled up and now works for millions of transistors."

But after a point, cranking up the clock speed becomes an exercise in diminishing returns. That's why a one-gigahertz chip doesn't run twice as fast as a 500-megahertz chip. The clock, through the work it must do to coordinate mil-

lions of transistors on a chip, generates its own overhead. The faster the clock, the greater the overhead becomes. The clock in a state-of-the-art microprocessor can consume up to 30 percent of the chip's computing capability, with that percentage increasing at an ever faster rate as clock speeds increase. It's as if a factory became overrun with stopwatch-wielding supervisors who improved efficiency but also took up more and more space held by workers and machines.

Clocked chips are becoming serious power hogs, too: the job of coordinating tens of millions of transistors at a billion ticks per second requires the consumption of a lot of energy, most of which ends up as heat. Patrick Gelsinger, chief technology officer at Intel, referred to the problem in his keynote speech at the International Solid-State Circuits Conference last February. Gelsinger was only half-joking when he said that if microprocessors continue to be run by ever faster clocks, then by 2005 a chip will run as hot as a nuclear reactor.

Perhaps the most pressing problem with conventional microprocessors, though, is that you can only speed up the chip's clock so much before banging into some inconvenient physical realities. In today's one-gigahertz chips, electronic pulses signifying binary ones and zeroes can—just barely—make it across the chip within a single beat of the clock. But in the two-gigahertz chips expected to arrive in the next couple of years that will no longer be true. The role the clock plays now, synchronizing all the work on a chip, will begin to break down.

Clockless to the Rescue

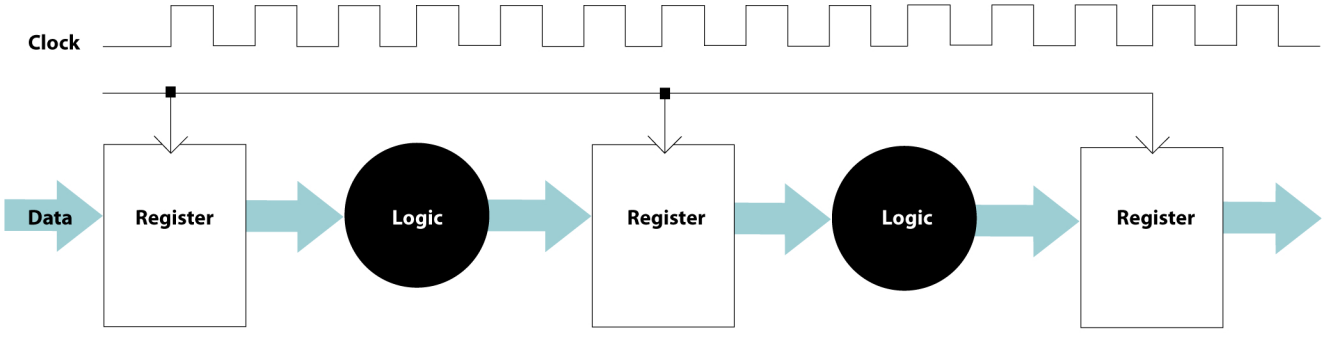
By throwing out the clock, chip makers will be able to escape from this bind. Clockless chips draw power only when there is useful work to do, enabling a huge savings in battery-driven devices; an asynchronous-chip-based pager marketed by Philips Electronics, for example, runs almost twice as long as competitors' products, which use conventional clocked chips.

Like a team of horses that can only run as fast as its slowest member, a clocked chip can run no faster than its most slothful piece of logic; the answer isn't guaranteed until every part completes its work. By contrast, the transistors on an asynchronous chip can swap information independently, without needing to wait for everything else. The result? Instead of the entire chip running at the speed of its slowest components, it can run at the *average* speed of *all* components. At both Intel and Sun, this approach has led to prototype chips that run two to three times faster than comparable products using conventional circuitry.

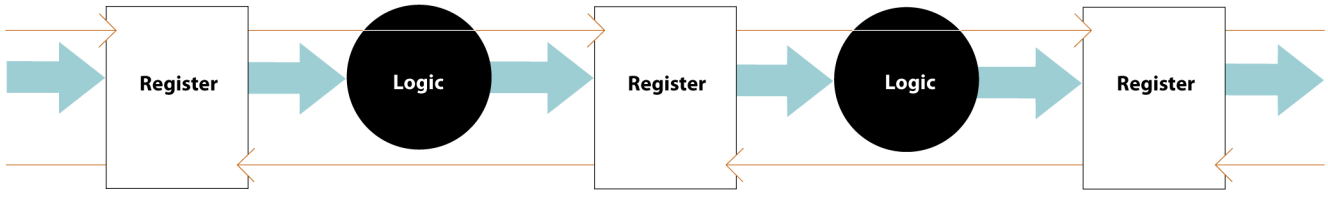
"Look at it this way," says Intel's Ebergen. "You give me a folder, I work on it, I give it back to you, and the fact that I give it back indicates I'm done. We don't have to communicate every five seconds. We might do the job much faster by agreeing between the two of us when to get things started and when to get things done and not worry about synchronizing our work every step along the way."

Another advantage of clockless chips is that they give off very low levels of electromagnetic noise. The faster the clock, the more difficult it is to prevent a device from interfering with other devices; dispensing with the clock all but eliminates this problem. The combination of low noise and low power consumption makes asynchronous chips a natural choice for mobile devices. "The low-hanging fruit for clockless chips will be in communications devices," starting with cell phones, says Yobie Benjamin, a

Clocked vs. Clockless



CONVENTIONAL CHIPS operate under the control of a central clock, which samples data in the registers at precisely timed intervals.



CLOCKLESS CHIPS dispense with the timepiece. In one scheme, data moves instead under the control of local "handshake" signals (orange lines, above) that indicate when work has been completed and is ready for the next logic operation.

SOURCE: UNIVERSITY OF MANCHESTER, DEPARTMENT OF COMPUTER SCIENCE

Losing Time

It's taken more than 60 years, but clockless chips are finally finding their way into the market.

1940 1960 1980 2000

Late 1940s
Alan Turing and other early computer developers consider and reject asynchronous designs, choosing to use clocks to ensure more reliable operation.

1960s
The idea of clockless chips all but disappears, kept alive only by a few esoteric papers from academics.

1989
Computer graphics pioneer Ivan Sutherland writes a paper that reignites interest in clockless-chip technology.

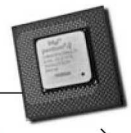
1989
Caltech computer scientist Alain Martin builds the first clockless microprocessor.

1990
The University of Manchester (England) begins an asynchronous research group.

1994
The Manchester group, led by Steve Furber, produces an asynchronous chip compatible with cell phones made by ARM.

1997
Intel develops an asynchronous, Pentium-compatible test chip that runs three times as fast, on half the power, as its synchronous equivalent. The device never makes it out of the lab.

1998
Philips introduces a commercial clockless chip, the first to market, which lets the company's pagers last nearly twice as long on the same battery power.



2001
Intel introduces the Pentium 4 microprocessor, which incorporates some clockless elements.

TIMEPIX (PENTIUM 4 CHIP); PORTRAITS COURTESY OF THEIR SUBJECTS

technology strategist for the consulting firm Ernst and Young. So convinced is Benjamin of the technology's promise that he has personally invested in Asynchronous Digital Design, a clockless startup out of Caltech.

Two other new firms, Theseus and Manchester, England-based Self-Timed Solutions, are focusing on clockless chips for smart cards. Fant maintains that a key problem holding back smart cards is that conventional chips make it easy to crack the chip's security codes by watching the signals. "The clock is like a big signal that says, 'Okay, look now,'" says Fant. "It's like looking for someone in a marching band. Asynchronous is more like a milling crowd. There's no clear signal to watch. Potential hackers don't know where to begin."

Speed, energy efficiency and stealth sound like important goals for any chip, not just those used in a few niche applications. But while Sun, IBM and Intel all have small research groups working on asynchronous designs for specialty applications, neither they nor anyone else has announced work on a general-purpose clockless microprocessor. This seems an odd oversight. An industry that considers the improvement of processor speed to be an almost sacred goal has forsaken one of the most promising avenues for making chips go faster. You just have to ask why.

Why, for example, did Intel scrap its asynchronous chip? The answer is that although the chip ran three times as fast and used half the electrical power as clocked counterparts, that wasn't enough of an improvement to justify a shift to a radical technology. An asynchronous chip in the lab might be years ahead of any synchronous design, but the design, testing and manufacturing systems that support conventional microprocessor production still have about a 20-year head start on anything that supports asynchronous production. Anyone planning to develop a clockless chip will need to find a way to short-circuit that lead.

"If you get three times the power going with an asynchronous design, but it takes you five times as long to get to the market—well, you lose," says Intel senior scientist Ken Stevens, who worked on the 1997 asynchronous project. "It's not enough to be a visionary, or to say how great this technology is. It all comes back to whether you can make it fast enough, and cheaply enough, and whether you can keep doing it year after year."

Philips's asynchronous chip has given the company's pagers the ability to last almost twice as long, on the same battery power, as clocked alternatives. But its debut in 1998 followed a decade of dedicated research. Asynchronous researchers from the beginning understood that their task wasn't just to build another chip, but rather to build a way to design, test and manufacture that chip. And that wasn't easy.

Playing Catch-Up

The first huge barrier to bringing clockless chips to market is the lack of automated tools to accelerate their design. Twenty years ago, a handful of engineers could lay out a chip's circuitry on paper. Today, hundreds of engineers work in teams, and the only hope of coordinating their actions is to use sophisticated computer-aided tools. But asynchronous designers face a chicken-and-egg problem: if there is no mass market for asynchronous chips, there's little incentive to create tools to build them; if there are no tools, no chips get produced. The same problem applies to the development of chip-testing technologies. Without any significant quantity of asynchronous circuits to test, there is no market for third-party testing tools.

In the case of its pager chips, Philips decided the only way out of this trap was to itself invest in developing the tools it needed. "After 13 years of research, we are now close to an effective and efficient test approach for asynchronous circuits," says Philips research fellow Kees van Berkel, who has worked on the Dutch giant's asynchronous team since the early 1980s. And

Philips is not alone in this quest. In an effort to create momentum for asynchronous chips, two computer scientists—Steven Nowick at Columbia University and Steve Furber at the University of Manchester—have each developed design tools that they are giving away as shareware. "Tools are now the show stoppers," says Nowick. "If you don't have tools you can't do things in portable ways, and you can't train people to become experts."

Beyond a new generation of design-and-testing equipment, successful development of clockless chips requires people who understand asynchronous design. Such talent is scarce, as asynchronous principles fly in the face of the way almost every university teaches its engineering students. Conventional chips can have values arrive at a register incorrectly and out of sequence; but in a clockless chip, the values that arrive in registers must be correct the first time. One way to achieve this goal is to pay close attention to such details as the lengths of the wires and the number of logic gates connected to a given register, thereby assuring that signals travel to the register in the proper logical sequence. But that means being far more meticulous about the physical design than synchronous designers have been trained to be.

An alternative, used by Theseus and others, is to open up a separate communication channel on the chip. Clocked chips represent ones and zeroes using low and high voltages on a single wire; "dual-rail" circuits, on the other hand, use two wires, giving the chip communications pathways, not only to send bits, but also to send "handshake" signals to indicate when work has been completed. Fant additionally proposes replacing the conventional system of digital logic with what he calls "null convention logic," a scheme that identifies not only "yes" and "no," but also "no answer yet"—a convenient way for clockless chips to recognize when an operation has not yet been completed. All of these ideas and approaches are different enough that executing them could confound the mind of an engineer trained to design to the beat of a clock. It's no surprise that the two newest asynchronous startups, Asynchronous Digital Devices and Self-Timed Solutions, are populated by students coming out of Caltech and the University of Manchester, where clockless-chip research has been going on the longest.

For a chip to be successful, all three elements—design tools, manufacturing efficiency and experienced designers—need to come together. The asynchronous cadre has "very promising ideas," says Max Baron, microprocessor analyst and editor of the industry newsletter *Microprocessor Report*. "But they don't have the actual machine, and they haven't proven they know how to build it."

Though it will take far longer for clockless chips to go mainstream, we're already seeing the beginnings of that transition as well. Intel, which shelved its asynchronous-chips project in 1997, incorporated elements of its clockless technology into the Pentium 4 chip that it released this year. "We're introducing asynchronous design from the bottom up, designing in some pieces of unclocked logic in a chip that is still of conventional design," says Stevens. "At this point, if we can do something asynchronously, and it's better in terms of power consumption, then we will do it."

So what of Karl Fant's flamboyantly predicted revolution? In an industry as mature as chip making, there's no replacing dictatorship with anarchy overnight. But over time, the balance will probably shift toward clockless design; enough articles will be written, enough tools built, enough engineers educated that it will no longer be unrealistic to imagine marketing such a chip even outside of specialized niches. "Once people understand how to do this easily, it will become more natural to think about asynchronous," says Sun engineer Normoyle. "People won't do it because it's interesting. We'll do it because it's easier than something else. Our only goal is to be better than the other guys. The switch will come when synchronous is no longer good enough."

The winners in this next wave of innovation will be the companies that choose the right time to jump off the curve. Clockless chips have the promise of revolutionizing the industry, of rapidly accelerating the relentless drive toward faster and cheaper chips that we've come to expect from Moore's Law. Who is to say what might be possible? Why not an all-asynchronous chip compatible with Intel products?

"If someone does that, they will have a serious competitive advantage for a number of years," says Intel's Stevens. Translation? "So yeah, we're worried."

Let the anarchy begin.

Clockless Companies

COMPANY	CLOCKLESS ACHIEVEMENTS	GOALS
SUN MICROSYSTEMS Palo Alto, CA	Prototypes have demonstrated two to three times the speed of standard chips.	Gradually integrate "islands" of clockless logic into future generations of microprocessors.
INTEL Santa Clara, CA	Clockless prototype in 1997 ran three times faster than the conventional-chip equivalent, on half the power.	Stay current with clockless R&D.
ASYNCHRONOUS DIGITAL DESIGN Pasadena, CA	Founded by students of Caltech's Alain Martin, who developed the first asynchronous microprocessor.	Produce chips for cell phones and other low-power communications devices; expected to announce plans by year-end.
THESEUS LOGIC Maitland, FL	Patented "null convention logic," a way of letting clockless chips know when an operation is complete.	License designs to manufacturers of smart cards and mobile devices; Motorola is a current customer.
PHILIPS ELECTRONICS Eindhoven, the Netherlands	Markets a clockless chip that gives its pagers up to twice the battery life of competitors.	Clockless chips for mobile devices and smart cards.
SELF-TIMED SOLUTIONS Manchester, England	Founded this fall by Steve Furber of the University of Manchester, who has developed clockless chips for communications devices.	Clockless chips for smart cards.

It gave us the Internet and the mouse. Today, the U.S. Defense Advanced Research Projects Agency remains a powerful engine driving technological change.

BY DAVID TALBOT / PHOTOGRAPHS BY MISHA GRAVENOR

DARPA'S DISRUPTIVE TECHNOLOGIES

Robo-warrior: Loaded with sensors and cameras, this meter-high test robot needs sophisticated software if it's going to coordinate with armies of robots, unmanned aircraft and soldiers in a future battle. DARPA is working on just that.

NOTHING QUITE LIKE IT HAD EVER BEEN ATTEMPTED. DEEP IN THE CALIFORNIA DESERT LAST MARCH, AS A FEW FATIGUES-CLAD U.S. MARINES STOOD NEARBY, RESEARCHERS FROM THE UNIVERSITY OF CALIFORNIA, BERKELEY, FIDDLED WITH A 1.5-METER AIRPLANE WITH SIX WALNUT-SIZED BUNDLES OF ELECTRONICS ATTACHED TO THE UNDERSIDES OF ITS WINGS. EACH BUNDLE, SWADDLED IN PINK PLASTIC, HELD A MAGNETIC-FIELD SENSOR, SHORT-RANGE RADIO TRANSMITTER, ANTENNA AND MICROPROCESSOR RUN BY A CUSTOM LOW-POWERED OPERATING SYSTEM DUBBED "TINY OS."

And then the remote-controlled plane, freighted with the early embodiments of a hoped-for advance in miniaturized, networked sensing, buzzed aloft, traveled about two kilometers and dropped its pink payload along a dirt road. Soon, as planned, a few trucks drove past the innocuous electronic spies. The bundles detected the trucks' magnetic fields, shared this information among themselves and beamed a report on the vehicles' location, speed and direction to the remote-controlled plane circling overhead. The aircraft, in turn, relayed the news to the researchers and soldiers waiting on the rugged terrain of the Marine Corps base in Twentynine Palms, CA.

The bundles were crude prototypes, and it took days to get even this limited experiment right. But someday thousands of similar devices—only much tinier, perhaps as small as dust motes—might be deployed to collect and process a rich array of information about enemy movements, crop conditions, pollution or anything else requiring monitoring. Realizing such a vision will demand advances in everything from microscale sensors to materials to programming. It's a huge undertaking. But there's a common benefactor: the U.S. Defense Advanced Research Projects Agency, which brokered the desert experiment and is funding ambitious investigations into each of the technologies involved.

Commonly known as DARPA, this is the U.S. Department of Defense's storied outpost of technology research—military systems, yes, but also innovations that sometimes create and transform industries. Formed in 1958, in the technological frenzy sparked by the Soviet Union's launch of its Sputnik satellite, DARPA boasts a four-decade-long history of promoting novel technologies—today doling out nearly $2 billion annually to corporate, government and university researchers in support of high-risk, potentially high-impact ideas. Among its many successes *(see "Four Decades of Success," p. 45)*, DARPA's gambles proved instrumental in spawning the Internet and the computer mouse, stealth aircraft and the chip that makes your cell phone work—advances that meant research as out-of-the-box in its time as dust-mote-sized sensors seem today.

DARPA is hardly the only player funding cutting-edge research—think National Science Foundation or National Institutes of Health—and certainly not the deepest pocketed. But the agency's swashbuckling style of betting on seemingly far-out research—and bringing together interdisciplinary teams that it pushes toward a practical advance—sets it apart. And while some contend that DARPA has moved back from the cutting edge in recent years, concentrating too much on short-term military issues rather than truly breakthrough ideas, no one denies that the agency remains a powerful engine of technological change. "An awful lot of the good stuff we have today is there because DARPA was willing to take a chance on visionary projects," says David Waltz, president of the NEC Research Institute in Princeton, NJ. "They are *the* visionary agency."

MUNDANE POWERHOUSE

In its physical aspect, DARPA is nothing if not mundane. The critical decisions that agency officials make on exotic technologies are rendered in an unremarkable leased office building in Arlington, VA. There are no labs here; DARPA is a funding agency, not a research facility. No sign advertises DARPA's tenancy to passersby. Except for the anti-eavesdropping gadgets glued to its conference-room windows, this edifice of black-hued glass could pass for an insurance company. But once in the lobby, newcomers must submit their social security numbers to "Visitor Control." Guards ask, "classified or unclassified?" and make sure guests stay in sight (around here, it's a no-no to wander into a hallway in search of the water cooler, and telephones bear labels warning that conversations are recorded).

The offices are filled with about 240 employees, of whom half are technical staff—program managers whose job is to shape the work DARPA funds and scour the country for promising new ideas. In keeping with DARPA's antibureaucratic ethos, these managers are not career government employees but experts on loan from universities, corporations and federal research labs, pulling stints at DARPA of between three and five years. "DARPA is the [Department of Defense's] center for revolutionary ideas. It is a true bottom-up organization where program managers are the heart and soul," says Anthony J. Tether, the agency's director. "We hire people who have a dream that they cannot get fulfilled elsewhere....DARPA program managers are by nature risktakers; they are passionate about making a difference."

It is in the arena of emerging technologies—funding for research makes up 56 percent of the agency's $2.2 billion 2002 budget—that the greatest triumphs have come. And a look at the agency's current lineup shows plenty of potential for future successes. Want microscopically small machines? DARPA was an early funder of efforts to produce miniature mirrors, sensors and gauges—devices used in so-called microelectromechanical systems (MEMS)—that are now widely employed in industry. Want tiny, low-powered computers? DARPA is backing work on logic and memory components as small as individual molecules. Want thousands of sensors (or little robots) to synthesize observations and coordinate actions? DARPA is funding the networking technologies and software they'll need. Want something to quickly detect tiny amounts of viruses and other pathogens? DARPA is working on that, too, and a lot more.

It all adds up to a diverse panoply of projects, but the principle on which they are chosen is the same: "We're about surprise. Prevent surprise, and create surprise," says Jane Alexander, the agency's deputy director. "You need a skunk works, somebody over in the corner who is anticipating what your opponent is doing and what you are going to answer that with, and also is anticipating what your next generation is—what are you going to surprise somebody with. DARPA is that thing."

But the key to the agency's success lies not so much in its mission as in its unique administrative model and management philosophy. For starters, before DARPA officials even decide what to fund, "one of the questions senior management asks is, 'Is somebody else able to do this problem?' If they are, let them do it," says Alexander. And if not, DARPA primes the pump—providing enough time and money for the technology to take root in the commercial world. "With the right investment at the right time, I can steer industry toward an area that will be useful. I nudge them."

These are multimillion-dollar nudges, of course, so the aim is to choose carefully. After hearing from the military about its near- and long-term needs, DARPA's program managers design multidisciplinary programs to help meet them. Major initiatives—or "thrusts"—usually last four years and incorporate five to 10 research teams; funding typically runs between $10 million and $40 million, and occasionally much more. Whatever the scale, though, DARPA stresses teamwork among research groups and enforces short-term performance milestones. And then, just as feverishly as DARPA begins a thrust, it often pulls out. Either the teams are unable to meet their goals, or they succeed sufficiently that the commercial sector or other research- funding sources pick up the ball. Alex Roland, a Duke University professor of military and technology history, says 85 percent of the agency's programs fail. "It's not an aspect of what they do that they want publicly displayed." Roland says. However, he adds, "You've got to expect a high rate of failure because the payoffs are fabulous."

So where will the next big successes come from? *TR* canvassed DARPA directors to identify today's hottest research projects. There's no guarantee any will pan out. But together they provide a representative look at the agency's most cutting-edge initiatives—and the direction technology is heading.

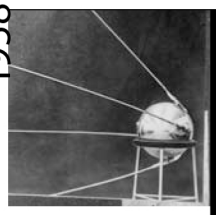
GLASSY METALS

Two seemingly unrelated events in early-1990s materials research have evolved into one of DARPA's most intriguing new areas of focus. One was the air force's ongoing quest for stronger, lighter materials to build better planes. The second exploded into view after the Persian Gulf War. During the conflict, United States-led forces used shells made of radioactive uranium-238 to attack Iraqi tanks. Instead of flattening on impact, uranium-238 peels away in layers and actually sharpens, making it more destructive than conventional shells. But some veterans' groups soon claimed the radioactive residue caused health problems. Plus there was an expensive environmental cleanup required. All this led the army to seek a nonradioactive replacement for its uranium projectiles.

In the mid-1990s, these parallel needs led DARPA to the Caltech lab of William L. Johnson, a pioneer in a field known as

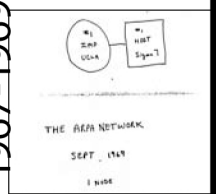
Four Decades of Success

Because many of the early-stage projects DARPA backs are also funded by other sources, crediting DARPA with specific breakthroughs is often difficult. But here are some key technology successes of the agency, which was known as the Advanced Research Projects Agency (ARPA) from 1958 to '72 and 1993 to '96, and DARPA from 1973 to '93 and 1996 to the present.

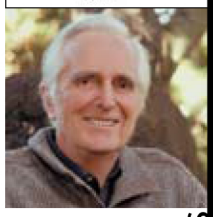


1958 In response to the Soviet Union's launch of Sputnik, President Eisenhower creates ARPA; order number one goes to German émigré rocket scientist Wernher von Braun to develop advanced boosters.

1962 Opens "Information Processing Techniques Office" led by J. C. R. Licklider, who moves computing beyond "arithmetic machines" by funding fundamental research in networking and time-sharing.



1967-1969 Funds development of the ARPAnet, a communication network designed to link remote military sites and ensure communications even in a nuclear attack. The precursor to the Internet is born.



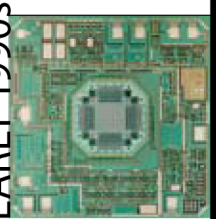
1968 Douglas Engelbart's ARPA-backed project to develop a new human-computer interface produces the mouse.

1970s Funds early work on the gallium arsenide semiconductors that become the brains of high-powered microwave devices, including cell phones.

1975 Launches programs to develop radar-absorbing materials, enabling future stealth aircraft.

1975-1980 Accelerates development of high-energy lasers for weapons use, including missile defense.

1980-1985 Funds improved lithographic manufacturing techniques to pack more transistors on silicon, leading to the "supercomputers on a chip" that power today's PCs.

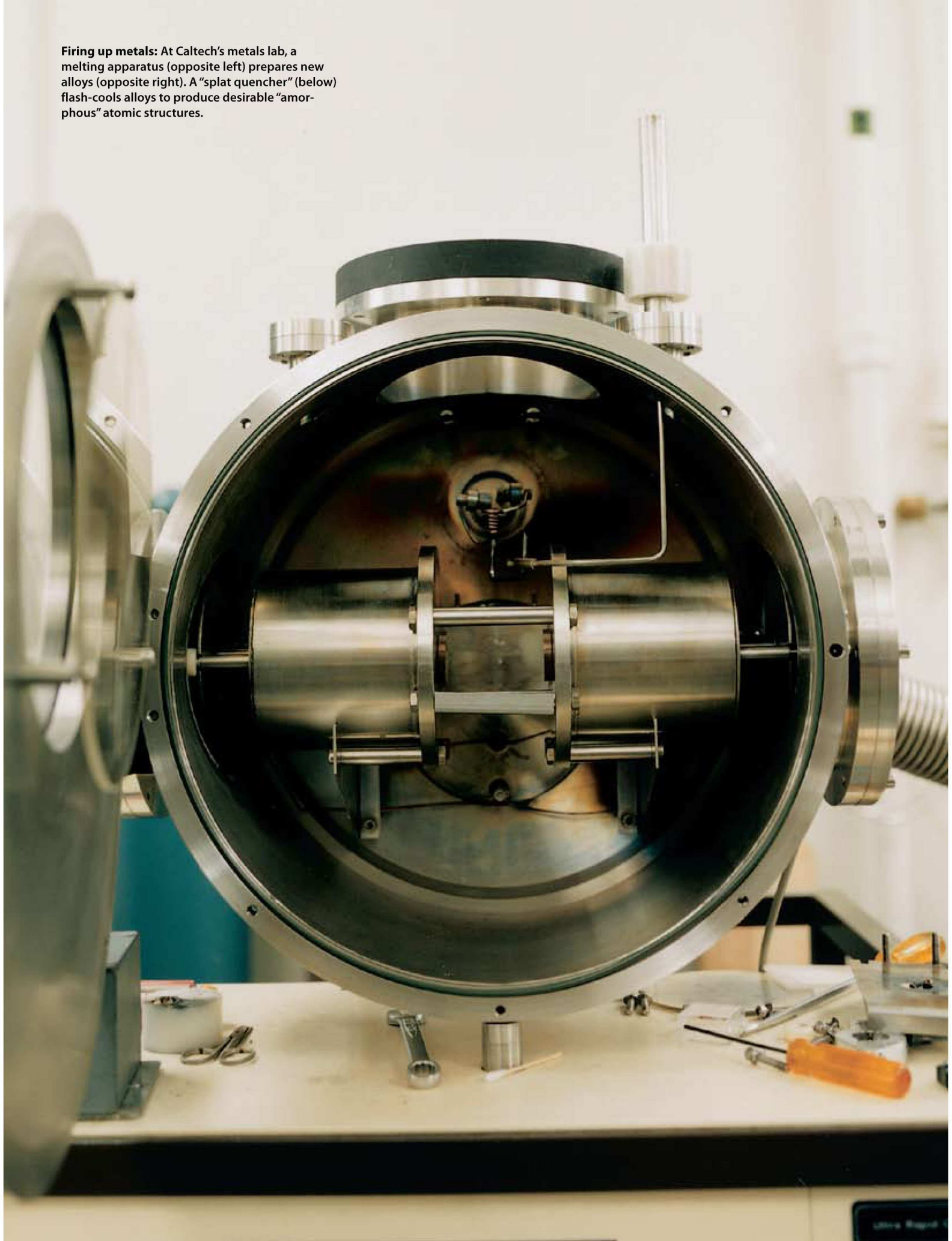


EARLY 1990s Funds work in microelectromechanical systems (MEMS), playing a key role in propelling micromachines to the marketplace.

1999 Supports broad efforts to find ways around potential limits of silicon semiconductors, including building computer elements out of individual molecules, jump-starting the field of "molecular electronics."

ANALOG DEVICES (MEMS); TIMEPIX (AIRCRAFT); THE COMPUTER MUSEUM HISTORY CENTER (ENGELBART AND ARPANET DIAGRAM); AP PHOTOS (SPUTNIK)

Firing up metals: At Caltech's metals lab, a melting apparatus (opposite left) prepares new alloys (opposite right). A "splat quencher" (below) flash-cools alloys to produce desirable "amorphous" atomic structures.



"glassy metals." Such materials look like ordinary metals, but they have a key difference: they've been fabricated so their atomic structures aren't orderly, or "crystalline," but rather random or "amorphous" in nature—like the atomic structure of glass. Scientists have known for at least a decade that a random atomic structure in a metal alloy can confer greater strength and more resistance to fracture and corrosion than are provided by crystalline structures, which contain more defects that make for weakness than amorphous structures. The problem is, glassy metals are extremely difficult and expensive to produce. In most cases, therefore, they have only existed as laboratory curiosities (an exception is Johnson's glassy zirconium-beryllium alloy, now used in high-end golf clubs). But working under army sponsorship, Johnson's lab in 1997 came up with a glassy tungsten that not only self-sharpened—making it a potential replacement for uranium shells—but pointed the way to techniques for mass-producing glassy metals with broader applications.

Looking to direct more firepower into this potential breakthrough area, DARPA this spring began a four-year, $30 million thrust to fund efforts to model the atomic interactions that take place as metals are mixed and cooled. The hope is that this insight will lead to glassy versions of widely used metals such as aluminum, titanium and iron that can be fabricated by the ton in existing factories. The first glassy metals were discovered "by trial and error, by happenstance, some might even say alchemy," says Leo Christodoulou, DARPA's manager of the new program, called Structural Amorphous Metals. "What we are trying to do is put [more] science behind this program, try to understand the fundamental physics."

DARPA's effort attacks the problem from several different angles. For starters, a team led by Johnson that includes seven university labs and three military research groups will do the underlying scientific studies and computational work and create new samples. The prototype materials will then be passed to industrial partners for small-scale fabrication and testing. (As of mid-August, the partner companies had not been announced.)

Whether any fundamentally new, factory-ready-metals recipes will emerge from this collaboration is an open question. But the potential payoff is clear: Johnson's group, for instance, is working on glassy aluminum and magnesium alloys that would possess twice the strength of their crystalline counterparts. That means less material would be needed to, say, build a fighter jet or a 747, enabling it to save fuel or carry heavier payloads. "If we can successfully do this, then this is the material aircraft will be built out of in 15 years," Johnson says. "It will become a major paradigm shift in the way we use metals."

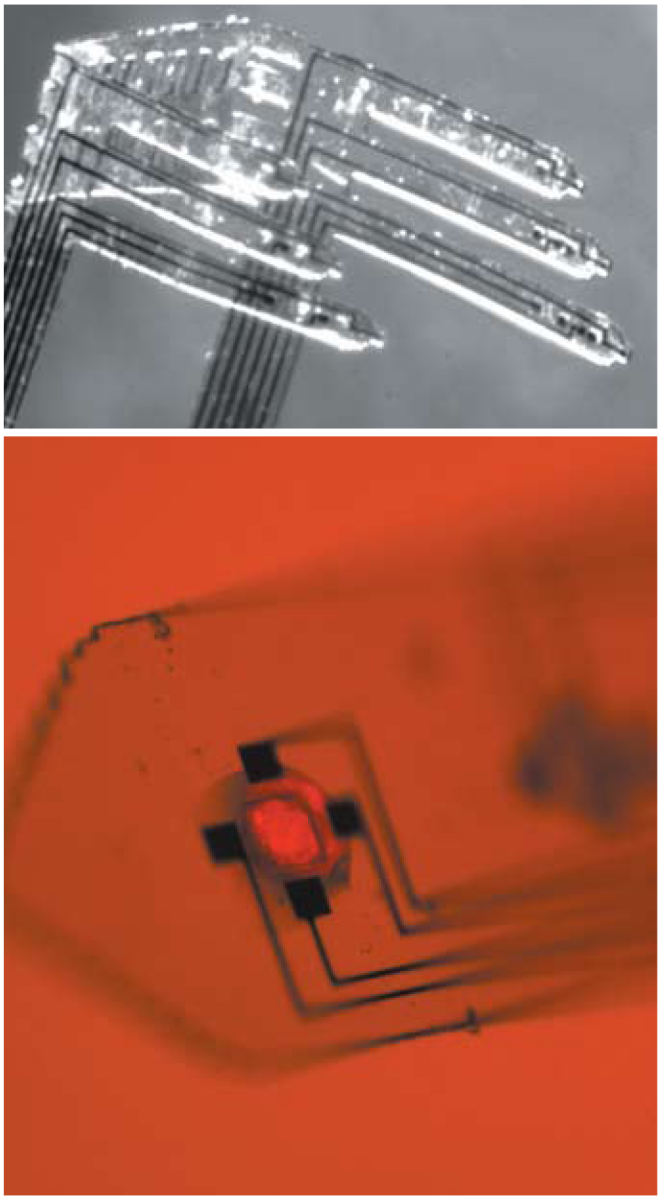
BIO:INFO:MICRO

The fusion of computing with other fields has become a given in recent years. The combination of computers and communications forms the basis of the Internet. The application of computing power to drug development has spurred bioinformatics and other, related areas of genomics and proteomics. In DARPA's view, the next challenge will be linking biology and computing to the science of the very small, through devices that can detect, influence, interpret and communicate what's happening in living cells. And so DARPA this year kicked off an ambitious $35 million, four-year effort called Bio:Info:Micro. As Alexander told a group of researchers last fall, there's a growing sense that merging biology with computing and microsystems "is something really new and revolutionary. In a lot of cases, we can't quite put our finger on it, but all of us, as technologists, think that this is a very promising area."

Two basic programs aim to fire early salvos in this predicted revolution. The first attempts to advance brain-machine interfaces—technologies that tap brain signals to control a variety of mechanical and electrical devices and can also send signals into the brain to stimulate neurons. This program has a solid starting point: already, DARPA-funded groups from Duke University, Caltech and elsewhere have built devices (tested only on animals so far) that can be surgically implanted in the brain to

detect neural signals and send those impulses via wires to computers. The computers decode the signals, then transmit control instructions to devices like robotic arms *(see "Brain-Machine Interface,"* TR *January/February 2001)*.

Linking brains to robotic arms is an awe-inspiring feat. But every component and process in these early systems needs loads of work. And that's where DARPA comes in. "We in the field have demonstrated the feasibility of direct communication with the brain," says Daryl Kipke, an associate professor of bioengineering at the University of Michigan who is leading one of three DARPA-funded university teams working on brain-machine interfaces. Now, he says, the challenge is to vastly improve this communication with help from the thrust's three basic disciplines. Kipke's team will work to improve existing MEMS implants, adding a microfluidic device to deliver drugs to the implant site. Biologists will seek to identify which molecules should be used to make neurons grow, stay healthy and not form scar tissue. And finally, computer scientists are improving brain-data processing.



COURTESY OF DARYL KIPKE, UNIVERSITY OF MICHI-

Brain probes: Advanced devices to intercept neural signals include an implant (top) built by Daryl Kipke that has six one-millimeter-long electrodes; the 150-micrometer-wide tip of another probe (bottom) built by Kipke's group includes a central drug-delivery reservoir.

If such systems ever get perfected, they could enable direct nervous-system control of prosthetic limbs, and even the realization of visions like mind-controlled mechanical "exoskeletons" that enable troops to exceed the limits of their normal strength and endurance, says Alan Rudolph, manager of DARPA programs developing robots based on biological designs. "The ability to have direct brain-to-machine links," he notes, "could in fact augment the ability of a human to deal with [all manner of] complex systems."

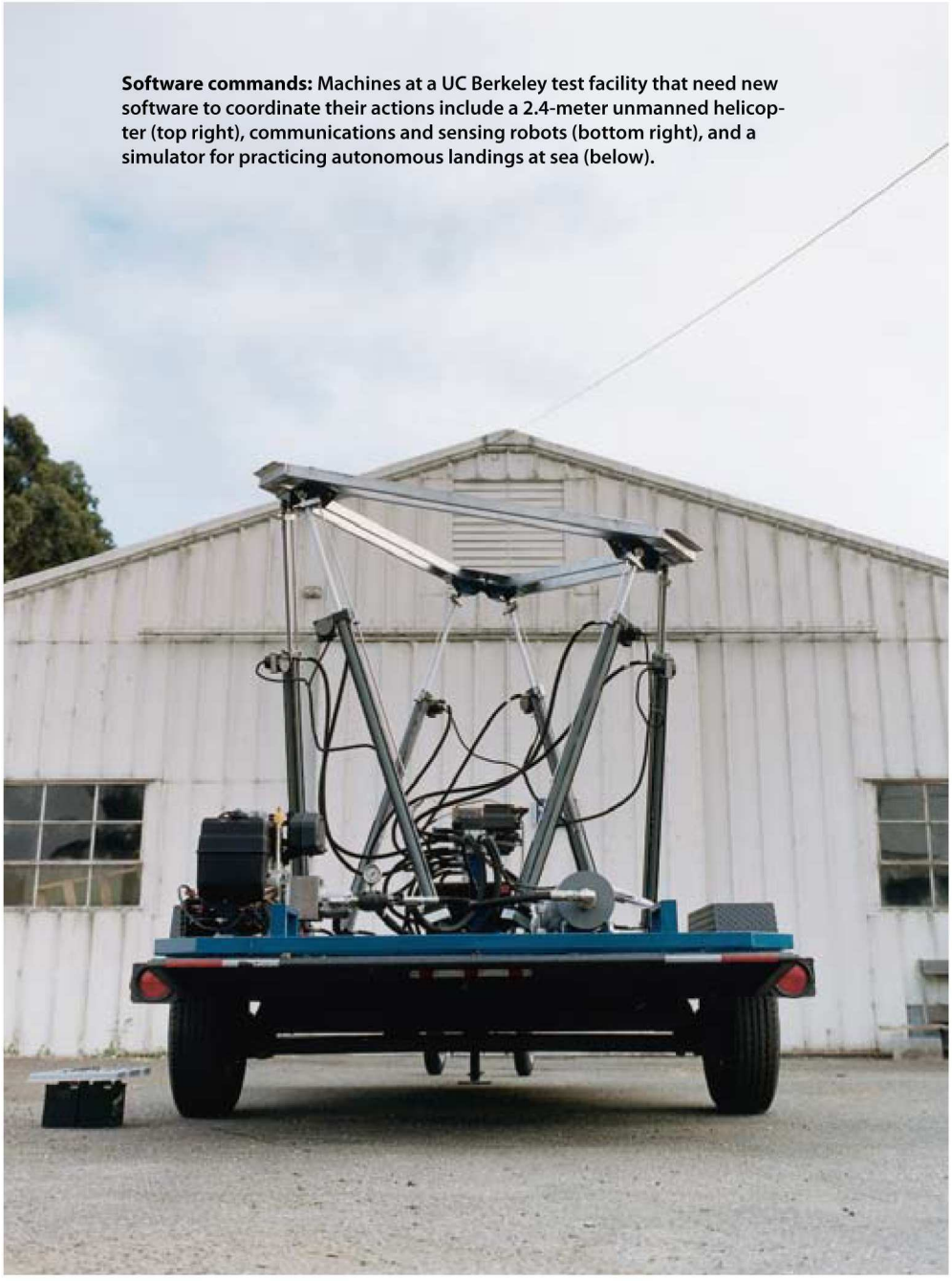
The second part of DARPA's Bio:Info:Micro program funds fundamental research aimed at advancing the understanding and control of one of life's most elemental components—the communication network within a cell. A collaboration at MIT, one of three universities where DARPA is funding such studies, includes an engineer aiming to perfect microfluidic devices that can quickly measure thousands of protein interactions, a biologist extracting the cellular proteins needed to detect these interactions—and computer scientists developing algorithms to make sense of the torrent of data that should result. While DARPA isn't the only group supporting these kinds of initiatives, "I'm not aware of other funding agencies…trying to advance all three of them simultaneously," says Douglas A. Lauffenburger, codirector of MIT's Division of Bioengineering and Environmental Health and leader of DARPA's Bio:Info:Micro team at MIT.

The work could point the way toward extremely sensitive sensors for detecting disease in the body or chemicals in the environment. It could also lead to new approaches to building complex systems—from robots to software—modeled after the extraordinary adaptability and ruggedness of ordinary cells. "Cells are designed to carry out very robust, reliable, simple sets of behaviors under highly variable, unpredictable conditions," says Lauffenburger. But the research is so fundamental, he adds, it's hard to predict what the first payoff might be.

AUTOMA-TEAMS

In a major report last year, the Joint Chiefs of Staff made clear their hope that robots would soon handle war's most dangerous tasks. Drone bombers would make early strikes. Robots would clear mines and even fire weapons. Tiny sensor-bots would spy on the enemy and look for evidence of chemical and biological weapons. But to realize this vision, the military needs a way to safely and reliably coordinate and control a robotic fleet that could number in the tens of thousands. It's a mind-boggling command and control problem, says Sharon Heise, a program manager in DARPA's Information Technology Office. "But the payoff is enormous if we can get it done."

With that in mind, DARPA recently announced a four-year, $65 million thrust called Mixed Initiative Control of Automa-Teams. The agency says the time is right for such a sweeping effort—uniting researchers in robotics, artificial intelligence and computer programming. Indeed, increasingly sophisticated robots for everything from mine clearing to air warfare have traveled far down the prototype pipeline, including a Boeing-built, DARPA-funded unmanned bomber that took its first flight test this summer. But many robots have been more impressive in their mechanics than in their software and control systems.



Software commands: Machines at a UC Berkeley test facility that need new software to coordinate their actions include a 2.4-meter unmanned helicopter (top right), communications and sensing robots (bottom right), and a simulator for practicing autonomous landings at sea (below).

The DARPA effort is so new that as of August no contractors had been named. But Heise doesn't need to issue contracts to know the immensity of the problem. The software required to control just one unmanned bomber is complex enough, she notes, integrating sensor data on parameters like wind speed, velocity and pitch, and then making a blaze of calculations and sending operating instructions to wing flaps, engines and bomb bay doors. "Now imagine expanding that to a number of vehicles. Now network those vehicles together. Now try to determine, how do you control those vehicles to a target?…the scaling happens so rapidly that it is very difficult to quantify."

DARPA's program doesn't seek to immediately provide all the answers—but rather to develop underlying theories of how to attack the problem. Explains Heise, "Those theories are implemented in fundamental mathematical algorithms, which are implemented in software and then demonstrated through modeling." DARPA expects this small-scale demonstration by 2005.

In many ways, the Automa-Teams project also gets to the heart of one of the most daunting issues in computing. That is, programming the actions of the thousands, if not millions, of massively distributed and often interconnected sensors and computer systems that will soon permeate everything from cell phones to cars to machinery to appliances. Already DARPA supports about a dozen programs in this "embedded computing" arena, of which Automa-Teams is just the latest. "Embedded computing is perhaps the biggest impact area of computing because it literally changes the physical environment around us," says Janos Sztipanovits, acting deputy director of DARPA's Information Technology Office. "It's a completely new software technology. That is where it gets quite exciting."

PLAYING FAVORITES

There's no disputing DARPA's past success or current ambition, but the agency is not without its critics. One complaint is that DARPA seems to disproportionately award its grants to a small universe of major universities, corporations and researchers. "I've heard complaints that DARPA plays favorites both with

people that it chooses for projects and the companies it selects as contractors. It's hard to break into the club," says NEC's Waltz. Another gripe, Waltz notes, is that DARPA managers can be a bit controlling and unreasonable. "DARPA, when they give you money, they feel they own your life. They call a meeting and expect you to drop everything and come and be prepared."

Waltz thinks such faults are forgivable in light of DARPA's historical output. But a more consistent—and fundamental—concern is that the agency has developed a shorter-term focus. "The biggest criticism that can be leveled at DARPA from the mid-1990s on is their telescope receded from distant galaxies to the nearby planets," says Kenneth Flamm, a Clinton-era Department of Defense official overseeing technology policy who now teaches at the University of Texas at Austin. During the Clinton administration, Flamm says, DARPA acceded to "pressure to show more military relevance."

Whether the Bush administration, with its emphasis on missile defense, cares to swing the pendulum toward more generic research remains to be seen. The challenge for DARPA, of course, is to promote technology's grandest dreams *and* show military relevance. Indeed, that's what was happening last March at the Marine Corps proving grounds, where Berkeley researchers demonstrated their walnut-sized electronic spies.

Six months later, the Berkeley group had almost finished building electronic bundles just one cubic millimeter in size—well on their way to creating the envisioned "smart dust" that could both help the military and revolutionize commercial monitoring and sensing. "Given where technology is headed, there is no question" that tiny networked sensors would have been invented someday, says Kris Pister, associate professor of electrical engineering at Berkeley. However, he adds, DARPA accelerates that process by promoting emerging technologies that are blue sky—but requiring them to fly in the desert sky.

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An Open Letter to DARPA

from Michael L. Dertouzos
Director, MIT Laboratory
for Computer Science

I HAVE OBSERVED THE AGENCY'S ACTIVITIES since 1963, first as a researcher and since 1974 as director of MIT's Laboratory for Computer Science. Now new leadership is taking over the agency. Here is an interesting question that may help them in their future plans: "What has been DARPA's return on investment in information technology?"

Over the first couple of decades of its existence, the agency invested some one billion of today's dollars in computer science and IT research. The return on that investment has included time-shared computers, packet radio and the early steps of the Ethernet, the ARPAnet and its successor the Internet, which made possible the World Wide Web, major advances in computer-aided design, especially of VLSI circuits, speech-understanding systems and many other key contributions in computer science and AI. By my reckoning, DARPA has been responsible for about one-half of the major innovations that have made information technology what it is today. And since IT economic activity around the globe today amounts to some two trillion dollars a year, we conclude that DARPA's return on investment has been around 1,000 to one, or in business terms 100,000 percent!

It's surprising how many people, especially in government, are unaware of how stellar this record has been, and underestimate DARPA's contribution to U.S. leadership worldwide—a position largely due to this nation's primacy in computers and information technology. Somehow, people still think of information technology as only a tool rather than as a principal strategic and economic asset that should be protected and enhanced. This mindset has even penetrated DARPA, which has begun reducing research in basic information technology, focusing instead on promising military applications of computers. The agency's previous leadership and Congress have concluded that they need not worry, since industry will "take care" of the more generic future IT research.

That is a pipe dream: take, for example, the development of a radically new operating system that would increase human productivity three to one, by making machines serve people rather than the other way around. It is against the interests of large software manufacturers to pursue such a research-and-development endeavor. They'd rather upgrade their systems incrementally so as to preserve a steady revenue stream from a huge base of existing customers. By doing so, they inadvertently exacerbate the complexity and difficulty of using these systems. A radically new approach could help all computer users in a big way, and could even save the U.S. Department of Defense tens of billion of dollars a year, through easier, more productive use of its many computer systems.

This kind of radical research is old hat to the DARPA community, whose "secret" success formula has been to tackle imaginative, high-risk research projects with a minimum of bureaucratic overhead and delays, while giving a great deal of latitude to capable researchers and program managers. Nearly all of the major innovations that came out of this proven approach have been on basic IT topics, and have helped military and commercial uses equally.

Information technology is still young and will continue to grow during the 21st century. Achieving a big return on investment through fundamental advances in the field is still in the cards. I urge the agency's new leadership to make basic IT a kingpin of future DARPA research within a well-balanced program of research and applications, and to reinstate the proven DARPA way of carrying out that research. This will go a long way toward enhancing U.S. military and economic leadership through information technology.

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TECHNOLOGY REVIEW

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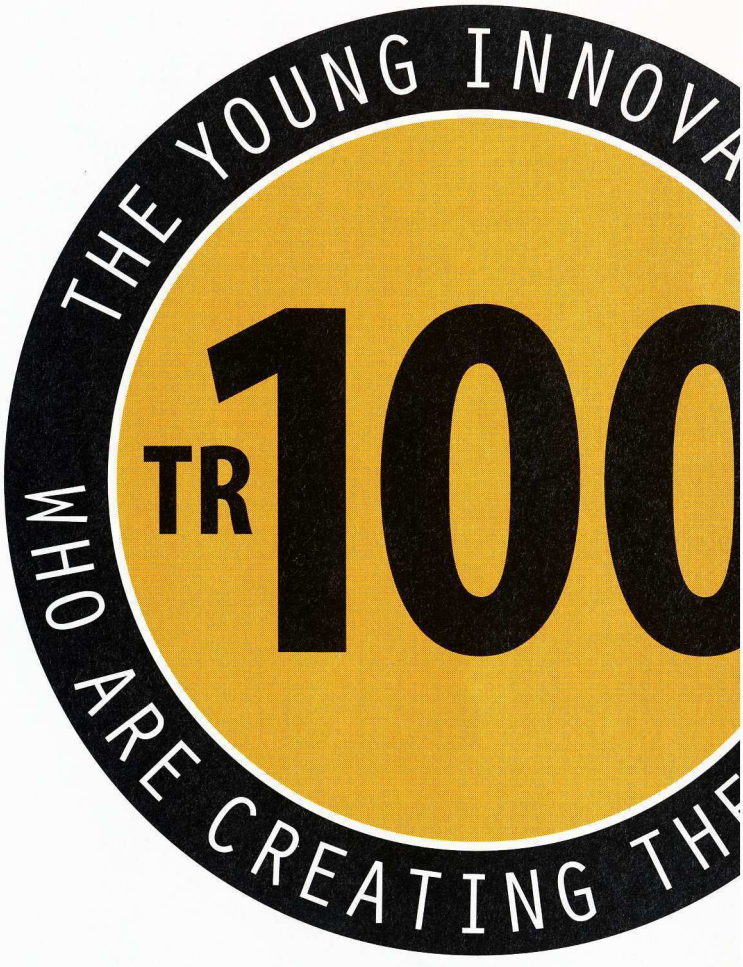

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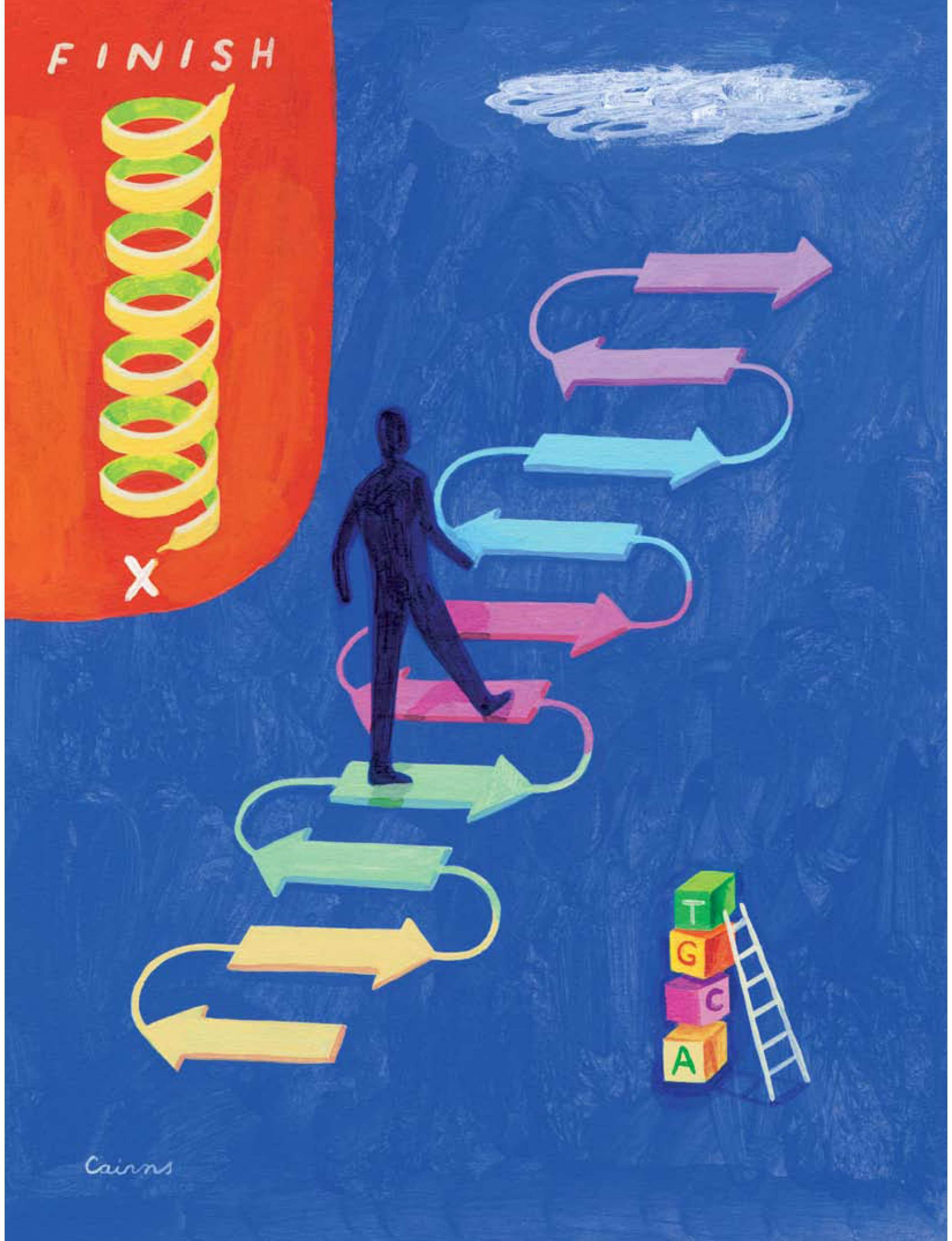
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NOW THAT THE HUMAN GENOME PROJECT IS DONE, PROTEINS ARE SET TO DISPLACE GENES AS THE NEW DARLINGS OF DRUG DISCOVERY. BUT ARE BIOLOGISTS UP TO THE TASK?

the proteomics payoff

On June 26, 2000, President Bill Clinton and Prime Minister Tony Blair jointly announced that researchers had completed the first draft of the human genome, a map that spelled out the three billion letters of the genetic code. "Without a doubt, this is the most important, most wondrous map ever produced by humankind," said Clinton. Blair was equally effusive. "Let us be in no doubt about what we are witnessing today—a revolution in medical science whose implications far surpass even the discovery of antibiotics, the first great technological triumph of the 21st century," said Blair.

But neither leader uttered a word that would soon take over the allure and promise that "genome" once enjoyed everywhere from the White House to Wall Street: "proteome."

Just as genomics is the attempt to decipher all of the genes in an organism, proteomics, in its simplest definition, aims to uncover all of the proteins and their functions. Since genes are simply the blueprints for proteins, which in turn are the main players in most of the body's functions, it's a logical progression. Indeed, there is no mistaking what proteomics promises: a revolution in medical science with implications that far surpass those of genomics.

BY JON COHEN
ILLUSTRATION BY BRIAN CAIRNS

Sounding an awful lot like the genomics gurus of yesteryear, proponents of proteomics declare that a "global understanding" of proteins will reveal the underlying mechanisms of disease, leading drugmakers to treatments that ablate causes rather than mask symptoms. Companies will discover a bounty of natural proteins that can serve as injectable drugs, the advocates assure, as well as an abundance of new protein targets for the "small-molecule" pills that are the cornerstone of the pharmaceutical industry. Side effects will plummet as the precision of treatments increases. A finer appreciation of the differences between the proteomes of individuals will allow doctors to tailor treatments to specific populations. And as new technologies emerge—your entire proteome on a chip?—medicine will advance in ways that even the most farsighted visionaries cannot imagine.

All of which has helped proteomics replace genomics as biology's new new thing. "Genomics is dead," declares N. Leigh Anderson, who heads Large Scale Biology's proteomics subsidiary in Germantown, MD.

Anderson and other proteomics enthusiasts argue genomics provides only rough clues about the workings of the body. And they question the many scientists who tightly tied the deciphering of the human genome to drug discovery. "To some extent, they've sold the public a bill of goods in genomics," says Anderson. Scott Patterson, who leads the proteomics project at Rockville, MD-based Celera Genomics, similarly sees serious shortcomings in some of the most celebrated drug-hunting strategies used by genomics companies—like studying arrays of genes without considering that the body modifies the proteins they code for in myriad ways. "Maybe everyone forgot their microbiology," says Patterson, whose company infamously raced (and goaded) the publicly funded Human Genome Project.

Investors, it appears, have not. Since June 26, 2000, more than $700 million has poured into proteomics companies from venture capitalists and IPOs. In addition to the swarm of startups that focus on proteomics, many genomics companies now have proteomics branches, and most every big pharmaceutical company has a proteomics-oriented biotech partner or has started its own proteomics division. And because proteomics makes heavy demands on computing power, deep-pocketed cyberstalwarts like IBM, Hitachi, Oracle, Compaq Computer and Sun Microsystems have joined in, too.

Still, not everyone shares the excitement. Some leading scientists worry that yet another bill of goods is being writ before their eyes. Sydney Brenner, who helped launch the Human Genome Project, says the proteomics craze is not about new knowledge but about amassing data—most of which he predicts will have no impact on drug discovery. "I think there will be a backlash," says Brenner, now at the Salk Institute for Biological Studies in La Jolla, CA. "I really think people will come to their senses. Science will just walk around them. [Proteomics] will prove to be irrelevant."

Even some proteomics leaders grimace at its popularity. "Today, many people try to use the word 'proteomics,' and I wish people did not like it so much," says Denis Hochstrasser, who does proteomics research at the University of Geneva in Switzerland and chairs the scientific advisory board for Evanston, IL-based startup GeneProt. "People expect too much from a buzzword, and they don't realize what's behind it."

For all its promise, proteomics remains strapped by serious limitations. The technologies to isolate and characterize proteins are still cumbersome and insensitive. Add to that the sheer vastness of the human proteome, and deciphering it presents an arrestingly complex mission. And while some academic and industry researchers have launched targeted efforts to tackle small bits of the puzzle, none resemble the organized effort to decode the human genome. "It's difficult to conceive of the idea of a human proteome project," says Celera's Patterson. "I just don't know when you'd ever say you finished. It's bad enough trying to figure out if you've finished the human genome project."

Yet the completion of the human genome does give proteomics an unambiguous starting point. Many new technologies have sprouted in the past few years that make it easier to find and identify proteins. And the detailed description of the human genome provides researchers working in proteomics a powerful new tool to chart, at least in a broad sense, the many technological and organizational challenges that lie ahead.

The Right Word

In mid-1994, Marc Wilkins, a student at Australia's Macquarie University, struggled to find the right words while cobbling together a scientific paper to support his PhD thesis on rapidly identifying proteins. Wilkins found himself repeatedly writing, "all proteins expressed by a genome, cell or tissue," a phrase he didn't like. "This was cumbersome, inelegant and made for a lot of extra typing," explains Wilkins, who now works at Sydney's Proteome Systems. So he started playing with words that would communicate the protein equivalent of the genome. After discarding "proteinome" and "protome," he settled on proteome, "the one that seemed to work best and roll off the tongue nicely."

In September 1994, Wilkins referred to the proteome at a scientific conference in Italy, and the word stuck.

Despite the similarities in the words, critical differences separate genomics

Some Proteomics Players

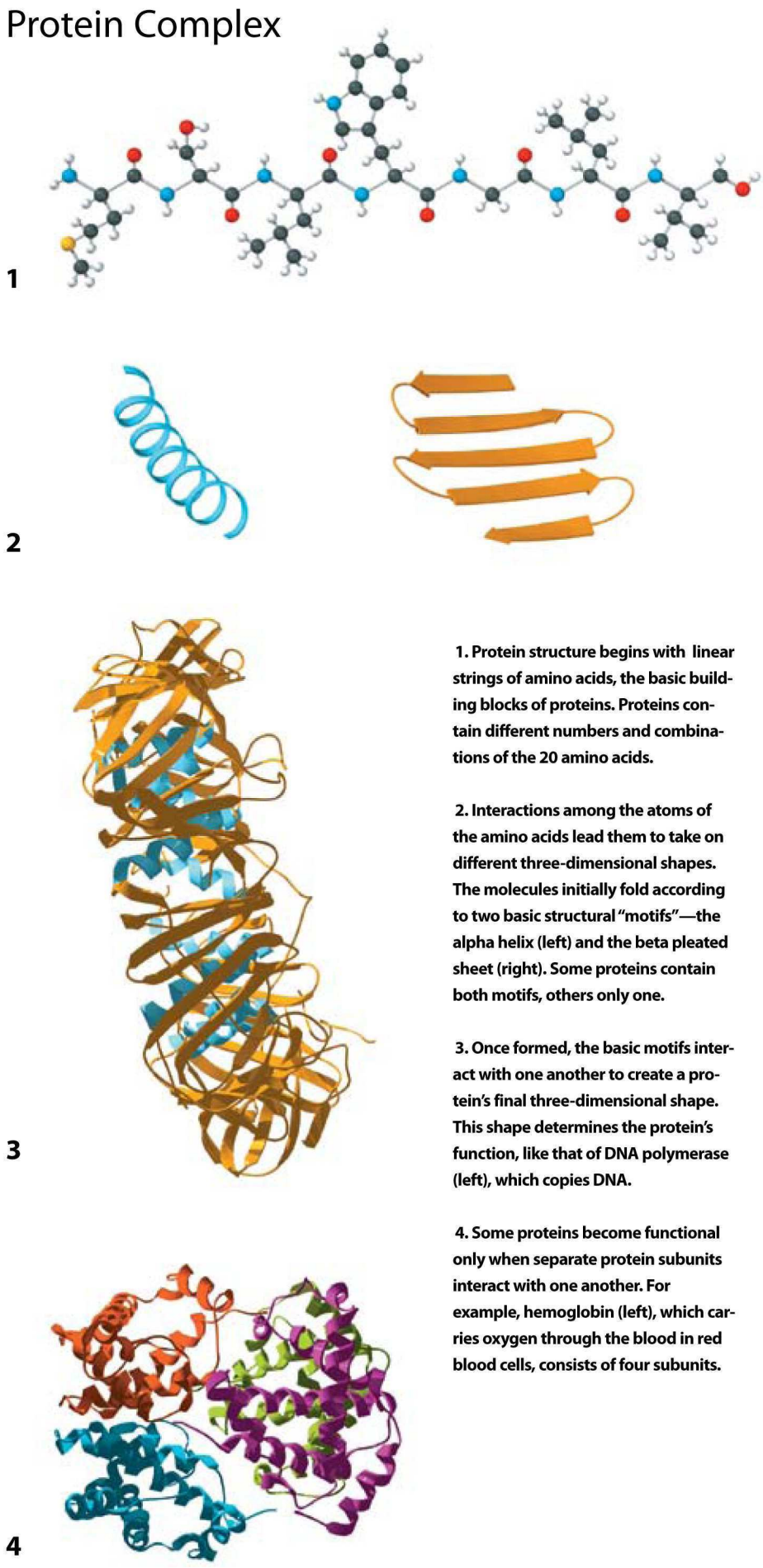
FOCUS	COMPANIES
Bioinformatics	Proteome Systems (Sydney, Australia), GeneProt (Evanston, IL)
Cell membranes	Celera Genomics (Rockville, MD)
Cell organelles	Caprion Pharmaceuticals (Montreal, Quebec)
Colon cancer	Europroteome (Hennigsdorf, Germany)
Protein chips	Zyomyx (Hayward, CA), Ciphergen Biosystems (Fremont, CA), Glaucus Proteomics (Bunnik, the Netherlands)
Protein interactions	Myriad Genetics (Salt Lake City, UT)
Protein structure	Accelrys (San Diego, CA), Structural GenomiX (San Diego, CA), Syrrx (San Diego, CA)

from proteomics, which give many investigators pause when the two are lumped together. "You can take DNA from anything—yourself, bananas, barnacles—and put it through a machine," explains Brenner. "That's because it's all the same stuff. There are no good techniques to try and handle proteins."

Proteins are far more complex than DNA on many levels. DNA consists of just four basic building blocks: adenine, guanine, cytosine and thymine. Various combinations of 20 different amino acids make up human proteins. The order in which *A*s, *G*s, *C*s and *T*s string together gives scientists the key to everything there is to know about genes, most of which have the same function: coding for proteins. In contrast, the three-dimensional shapes of proteins determine their functions, which seem endless. Proteins provide the structure of all cells and allow them to move around. They make up the cacophony of messengers that constantly traffic between immune-system cells, ordering some to battle and others to the barracks. They control the firing of neurotransmitters that allows us to think, the contraction of muscles that allows us to move, and the very on/off switches in our genes that allow us to make even more proteins. Proteins blow genes out of the water in sheer numbers, too. The Human Genome Project found between 30,000 and 40,000 genes scattered throughout our chromosomes. Estimates of the number of proteins in humans range from 60,000 into the millions; in other words, no one has a clue.

The relative simplicity and uniformity of DNA allowed scientists to develop powerful, fast, reliable tools to unravel the genome. Genomics owes much of its success to automated DNA sequencing; a state-of-the-art analyzer can sequence one million DNA letters in one day. Scientists also can amplify tiny amounts of DNA for easier study.

Protein scientists, in contrast, have no simple way to amplify, identify, quantify or characterize proteins. Instead, researchers must turn to a series of analytical instruments, few of which have been automated. Most proteomics efforts rely on two-dimensional gel electrophoresis to separate proteins; the technique pulls proteins away from each other based on their charge and mass. Mass spectrometry can then identify the proteins



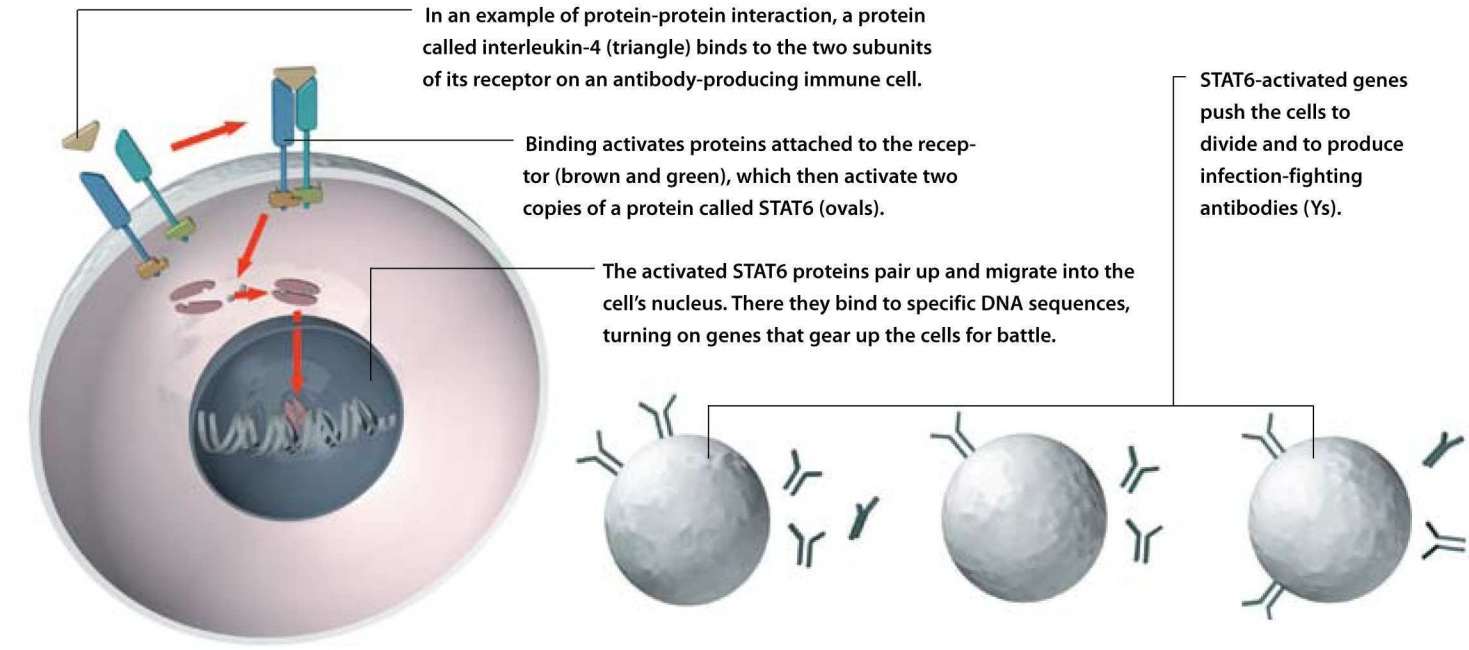
1. Protein structure begins with linear strings of amino acids, the basic building blocks of proteins. Proteins contain different numbers and combinations of the 20 amino acids.

2. Interactions among the atoms of the amino acids lead them to take on different three-dimensional shapes. The molecules initially fold according to two basic structural "motifs"—the alpha helix (left) and the beta pleated sheet (right). Some proteins contain both motifs, others only one.

3. Once formed, the basic motifs interact with one another to create a protein's final three-dimensional shape. This shape determines the protein's function, like that of DNA polymerase (left), which copies DNA.

4. Some proteins become functional only when separate protein subunits interact with one another. For example, hemoglobin (left), which carries oxygen through the blood in red blood cells, consists of four subunits.

Productive Pathways



JOHN MACNEILL

by analyzing their components. A technique called "yeast two-hybrid" tells researchers which proteins may interact with each other, while x-ray crystallography reveals a protein's three-dimensional structure. In short, no single technology rules the field the way the automated DNA sequencer has genomics, and it can take years to isolate, identify and determine the function of a single protein. There also remains no reliable way to amplify proteins, many of which appear in minute amounts. "And those [low-abundance] proteins are almost certainly the most important ones," says Brenner.

While the rise of genomics had much to do with the advent of new technologies *(see "Under Biology's Hood," TR September 2001)*, the ascent of proteomics has more to do with the limitations of genomics. Genomics companies routinely hunt for drug candidates by comparing which genes are turned on in healthy and diseased tissues or cells. Logically, if a company finds an overactive gene in, say, prostate tissue from a man who had prostate cancer, it might develop a drug that targets the protein that gene codes for. But here's the rub: a gene's level of activity can bear little relationship to the amount of the corresponding protein that gets made. "Looking broadly, there's no correlation," says Celera's Patterson. "Some of the correlation is negative, some of it's positive, and some we don't understand." Making such correlations even tougher, one gene can code for multiple proteins. And adding still more complexity, proteins go through elaborate modifications after they are formed, becoming—to name but a few examples—shrouded in sugars, studded with phosphates or cleaved.

For all the hoopla about proteomics, it has a long way to go before it proves itself as a great engine of drug discovery. "There still are very few deliverables on the ground, and people don't want to admit it," says Ian Humphery-Smith, a researcher at the Netherlands' University of Utrecht. And that's from one of the field's biggest boosters.

Human Proteome Project?

Humphery-Smith heads Glaucus Proteomics in the Netherlands and cofounded the Human Proteome Organisation, a nascent effort to get a human proteome project underway. "When you look at the start of the Human Genome Project, you had all this rhetoric about why it wouldn't work," says Humphery-Smith. "And I'm sure that we're ahead of where the Human Genome Project was in 1988. For one thing, we don't have to wait for funds: there are two billion dollars available now in industry and academia."

In June, the organization named its first president, Sam Hanash, a cancer proteomics researcher at the University of Michigan. Hanash tries to frame the group's mission in realistic terms. "It's impossible to conceive of a human proteome project that would be exhaustive, that covers everything that one would want to know about in relationship to the proteome," says Hanash. "But even if we cannot define a project that has an end, there's still a need…to define some components of an ill-defined project."

To Hanash, a human proteome project would describe all of the proteins and in what quantities they are expressed in all of the tissues of the body. Another way to look at the problem, then, is that each tissue has its own proteome. "You're talking about doing the Human Genome Project hundreds of times over," says Hanash. "It's very unrealistic to want to have as an objective for any one group or any one body to accomplish that. You're not going to see anyone say, 'We plan to complete the human proteome project,' the way Celera did with the genome project. It's not going to happen. If someone makes claims of that sort, they're misleading the world."

The Human Proteome Organisation's vision is to accomplish what one group cannot by coordinating what amount to multiple proteome projects that can feed off each other. Its goal is to catalogue every distinct human protein, all protein-protein interactions and levels of proteins in different cells and tissues. The organization would like to see all of this done in both healthy and diseased tissues and

cells. "There's a need to deconvolute this complexity," says Hanash. "Things are disorganized. If there's no consensus to emerge, no coordination, it will be too much of a frontier mentality."

Still, the prospect of a human proteome project is held back by a fundamental problem. Proteomics suffers from a technology gap that does not yet allow for the high-throughput, "massively parallel" analyses that have become the trademark of genomics. "The Human Genome Project was a particularly simple and get-your-hands-around-it definable goal, while proteomics is a far more amorphous and expandable area where we don't have breakthrough technologies yet," says biochemist Roger Tsien, whose own lab at the University of California, San Diego, is pushing forward the ability to image proteins as they move about cells *(see "Candid Camera," p. 60)*.

Tsien is part of what amounts to a mini proteome project. In September 2000, Alfred G. Gilman, a Nobel laureate at the University of Texas Southwestern Medical Center at Dallas, launched the Alliance for Cellular Signaling. The project includes more than 50 leading experts in such diverse arenas as fly and worm genetics, x-ray crystallography, bioinformatics and stem cells, but it has surprisingly discrete aims. The alliance over the next ten years wants to describe all of the proteins that interact to send signals from one part of the cell to another in two types of mouse cells, antibody-producing B lymphocytes and the myocytes that make up heart muscle. "We sort of want to know everything about a few things," says Marc Mumby, a researcher at UT Southwestern who heads the protein laboratory for the project. "It's a unique opportunity to bring together the expertise of a diverse group of people in a way that no one individual lab could do it."

Mumby stresses that the venture still does not truly amount to a proteomics project, even for these two cell types. Because the alliance aims to understand how proteins send signals, explains Mumby, the researchers only look at proteins that go through changes—the hallmark of a signal traveling through a cell. Many other "housekeeping" proteins exist that cells need just to stay alive.

Limited as it may be, the alliance's holistic approach has impressed many at the forefront of proteomics. "It's a much more exciting approach than trying to list all the proteins in any cell types," says Ruedi Aebersold, who last year left the University of Washington to cofound the Institute for Systems Biology in Seattle. "It's very close to how I think proteomics should be used—to capture dynamics of a system in a way that provides a global view." Adds Rochelle Long, a pharmacologist at the National Institute of General Medical Sciences, which awarded the alliance a $25 million grant, "It's a strike at the heart of proteomics."

The Fine Print

No proteomics companies have agendas that come anywhere near the type of comprehensive analysis favored by the Alliance for Cellular Signaling. But the companies' bold pronouncements about their projects would seem to indicate otherwise. Myriad Genetics of Salt Lake City, for example, announced in April that it had formed an alliance with Hitachi and Oracle "to map the human proteome in less than three years." Large Scale Biology is compiling a Human Protein Index that it boasts is "the protein equivalent of the Human Genome Project, in which all the proteins expressed by every human cell type are being documented." Celera's founder, J. Craig Venter, once declared that his company's proteomics division would work through "every tissue, organ and cell."

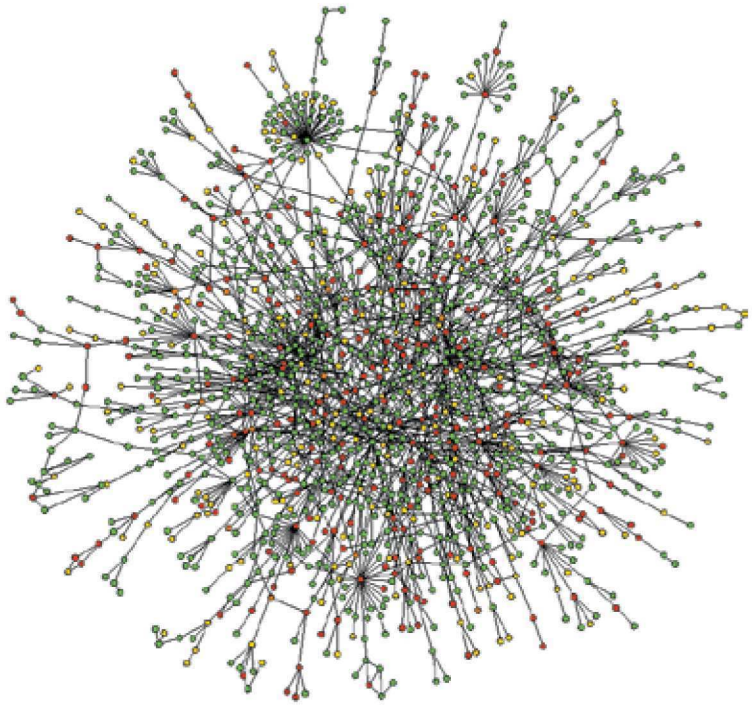
Many proteomics researchers blanch at these declarations. "Those are exaggerated claims, and you have to read the fine lines," says Human Proteome Organisation president Hanash.

What the fine lines reveal is that the more than 70 companies involved with proteomics are each exploiting limited technologies and therefore have sliced relatively small pieces of the human-proteome pie. Myriad's definition of proteomics, says executive vice president of research Sudhir Sahasrabudhe, is cataloguing all of the interactions between proteins that it can discover with yeast two-hybrid and mass spectrometry approaches. So much for a map of the human proteome in less than three years. In fact, Myriad has no intention of cataloguing all of the proteins in a human and their modifications. "The technology for conducting a comprehensive inventory of all proteins in a biological model is not there," says Sahasrabudhe. "You really just begin to skim the surface."

Meanwhile, Large Scale Biology has catalogued 115,000 proteins derived from

Making Connections

Mapping protein-protein interactions quickly becomes byzantine. The network below shows about three-quarters of the proteins (circles) from a single-celled yeast and their interactions.



COURTESY OF HAWOONG JEONG

157 "medically relevant" tissues in its Human Protein Index. Yet no one knows just how many medically relevant tissues there are. "We're in a quandary about that," acknowledges Anderson. "It's going to be an elastic concept," he says, based on the definition of what a separate tissue is. But whatever the definition, the effort seems far short of the boast of "the protein equivalent of the Human Genome Project." Anderson stresses that his company's goal is to develop new diagnostics and drugs rather than to know everything that can be known. "The Human Protein Index is trying to get down to a rational point that means something," he says.

Celera, too, now has much more circumscribed goals than finding all of the proteins from every tissue, organ and cell. Instead, the company studies tissues and cells from people with specific diseases and hunts for proteins found in the membranes that surround cells; such proteins are often susceptible to drugs. "We're looking in a very targeted way for potential therapeutics," says Patterson.

Other proteomics companies bill themselves—at least in the fine print—in relatively restricted terms as well. Some target proteins that work as enzymes, the molecular scissors that can cut other proteins and either cause or prevent disease. Other companies hunt for antibodies, the Y-shaped immune warriors that can glom onto dangerous proteins and render them harmless. Some, like Rockville, MD-based Human Genome Sciences, look for proteins secreted from cells *(see "Consulting Biotech's Oracle," p. 70)*. Still others carve out a bioinformatics niche, combing the literature to create novel protein databases, developing software to make sense of huge databanks, or helping companies design experiments to quickly find promising drug candidates.

And a dozen companies have invested heavily in developing the next hot assay in proteomics, protein affinity arrays *(see "Protein Chips," TR May 2001)*. These protein chips set up microgrids of protein fragments or molecules like antibodies that can trap proteins; one day, they may offer a fast, reliable way to compare hundreds of proteins found in, say, healthy and diseased tissue, giving researchers clues about how diseases develop and how drugs work.

Sydney Brenner, building on the oft-used analogy that the human genome data resemble the names and addresses found in a phone book's white pages, says all of these proteomics research efforts are attempting to compile yellow pages. "It's classification: we're trying to find all the plumbers," says Brenner. But he emphasizes that a true "global understanding" of the proteome will require much more. "We have to begin thinking about getting beyond the mere lists and the interactions," says Brenner. "That's as opaque as the original data. That's going to be the critical thing for biology. And it's not going to happen overnight."

The University of Geneva's Hochstrasser similarly sees the task as daunting. "It's funny when you think about it," Hochstrasser says. "People have sent a man to the moon. We have the entire human genome sequenced. But we do not know how many proteins we have in blood." And we may never know. "It's like the DNA world is finite, but maybe the protein world is infinite," he says.

So proteomics researchers may never enjoy their version of June 26, 2000, a day where they bask in the glory of heads of state exclaiming over the completion of their "map." But already, proteomics is revolutionizing the way scientists hunt for new medicines, and given the many diseases for which no good treatments exist, the ultimate payoff could be much larger than crossing a finish line. TR

Candid Camera

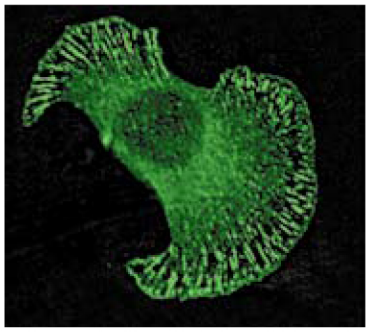
Hollywood stars may have more marquee value, but it was actors like calmodulin and myosin light-chain kinase that caught the eye of Roger Tsien.

A biochemist at the University of California, San Diego, Tsien helped pioneer techniques that effectively attach glow sticks to proteins so that microscopes outfitted with cameras can follow the proteins as they move about a cell. The results are elegant movies that promise to have an increasing impact as ever more biologists move beyond genomics and into the world of proteins.

"Genomics is just the cast list, and it's a cast of 30,000 in this enormous soap opera," explains Tsien. "We don't know what the screenplay is, and we certainly haven't seen it live, happening. Now we're beginning to see individual members of the cast kiss each other and do yet more impeachable offenses—shoot each other, or displace one another from each other's bed. It completely changes your view of what's going on with the biochemistry." In other words, imaging has the power to go beyond the who and the what, revealing the where, how and even the why.

The glow stick that imaging scientists rely on is green fluorescent protein, which comes from jellyfish. With genetic engineering, researchers can append the green marker to the proteins under study. Tsien's research, for example, focuses on the way calcium interacts with proteins like calmodulin and myosin light-chain kinase. Such interactions regulate everything from nerve cell growth to muscle movements.

John White, an imaging specialist at the University of Wisconsin-Madison, sees a bright future for biological movies. "It's still very much in its infancy, but I think there's a tremendous potential there," says White. He is particularly excited because of the limitations of other technologies driving proteomics, like the yeast two-hybrid screen used to find interactions between proteins. "You can do all the two-hybrids you can think of until you're blue in the face, but they don't tell you how the machine works," says White. "That information is useless unless you can visualize what's going on inside the cell."



COURTESY OF FRANK GERTLER

Glowing reviews: Green fluorescent protein helps show the structure of this mouse cell.

Tsien emphasizes that this technology is still labor intensive and often yields misleading results. "It takes a certain amount of skill, judgment and luck not to be fooled," Tsien says. He also cautions that imaging is not the way to hunt for proteins, which is simpler to do with other techniques.

But when a cast member is well known, Tsien says, "This is one of the most sophisticated techniques you can apply." And for biochemists intent on understanding the daily lives of proteins, maybe one of the most rewarding.

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Innovation gap: Venture capitalist Jurgen Drews warns that pharmaceutical firms aren't producing enough new drugs.

PHOTOGRAPH BY BETH PERKINS

SPEEDING DRUG DISCOVERY

GETTING A DRUG TO MARKET IS ALREADY EXPENSIVE AND TIME CONSUMING, AND A VAST NEW SURPLUS OF POTENTIAL DRUG TARGETS—COURTESY OF GENOMICS—THREATENS TO CLOG THE PIPELINE EVEN FURTHER. NEW INDUSTRIAL-SCALE BIOTECH EFFORTS COULD KEEP THINGS FLOWING.

BY GARY TAUBES

THE WOODLANDS, ABOUT 40 KILOMETERS NORTH of downtown Houston, is one of those planned communities that endeavors to provide virtually anything its residents might desire in an idyllic suburban setting. Among the Woodlands' five villages are bike paths and hiking trails, parks and golf courses, a shopping mall of Lone-Star-State proportions and an arts pavilion, not to mention a hospital, schools—and what may be the world's single largest genetically-engineered-mouse facility.

While the mice are not part of the careful plans of the community developers, they are key to the future of a local biotech company called Lexicon Genetics. Lexicon was founded six years ago by Arthur Sands and Allan Bradley, who were both at the Baylor College of Medicine at the time. Bradley is now director of the Sanger Centre in Cambridge, England, the largest European contributor to the Human Genome Project, while Sands stayed behind in Texas to run Lexicon and to tackle what he and Bradley assumed—rightly—would become the single most pressing issue in biology: Once the human genome is sequenced, what happens next? How is that copious information—the sequences of those 30,000 to 40,000 genes—transformed into medical therapies that will improve the lot of humankind?

"The genome encodes all potential drug targets for the pharmaceutical industry for all time," says Sands. "It's all there, encoded in the genes, which make proteins, which are the targets for drug discovery. Now we have the sequences. The big questions are, what do these genes do, and how do you mine the most valuable genes out of the genome for drug discovery?"

Lexicon's answer is mice: 300,000 of them. Specifically, "knock-out" mice, in which a single gene has been targeted and disabled. Biologists have used such mice for over a decade to illuminate the functions of genes by studying how the mice develop without them. Lexicon, however, has managed to industrialize and automate the knock-out production process, rolling out the high-tech mice the way Detroit does automobiles. What once took months, Lexicon can now do in hours. The company is presently churning out 1,500 such genetically compromised mice a week, which is why it's building its $40 million Woodlands mouse facility, the size of a few football fields, to hold them all.

It's this kind of massive, grand-scale effort that could represent the future of drug discovery in the postgenome world. In the same way that it took an automated, factory-like effort to sequence the human genome in the first place, biologists are now automating some of their favorite research tools—from mice to fruit flies to worms—to make sense of the mountain of new information. This biology at warp speed is, in effect, the mission of the science that has become known as "functional genomics." And for pharmaceutical companies facing the challenge of turning genomic information into actual drugs, functional-genomics tools are some of the hottest commodities around. To get their hands on as many of these tools as possible, drug firms are partnering with a number of biotech companies that, like Lexicon, promise to help unravel the genome's mysteries.

THE PHARMACEUTICAL INDUSTRY IS FACED WITH AN UNPRECEDENTED NUMBER OF OPPORTUNITIES TO DISCOVER NEW DRUGS—AND TO SPEND R&D DOLLARS. FROM A RECENT ANALYSIS COMES THIS DIRE WARNING: "THE INDUSTRY COULD GO BANKRUPT BY TRYING TO INNOVATE."

CLOGGED PIPELINE

For the past half-dozen years, drug industry experts such as venture capitalist Jurgen Drews, the former head of research at Hoffmann-La Roche, have been arguing that pharmaceutical companies are running perilously short on new drugs. Drews calls it "the innovation gap": by his calculation, each pharmaceutical company needs to bring at least one new drug to market every year, and preferably two or more, to survive and prosper. Instead, drug firms have been averaging considerably less—.4 to .8 new drugs per year per company.

The sequencing of the human genome should, in theory at least, solve one aspect of the innovation gap. After all, the entire pharmaceutical armamentarium—all the drugs against all the varieties of human illness—is aimed at a grand total of less than 500 biological targets, severely limiting the number of diseases that can be treated and the strategies used to do so. The information contained in the human genome, say Drews and others, is likely to increase the pool of potential drug targets 10- or 20-fold.

But that bounty will come at a considerable cost. The process of transforming some biologist's vision of a therapeutic gold mine into a new medication, certified by the U.S. Food and Drug Administration as safe and effective, is expensive and time consuming and getting more so every year. The latest estimate, from an analysis released in June by the Boston Consulting Group, suggests that pharmaceutical companies will spend about 15 years and $880 million for each novel drug that makes it to market.

First, a biological mechanism—a malfunctioning gene, for example, or the errant protein product of such a gene—has to be identified as critical to a disease process, and then that potential drug target has to be "validated," proven to be truly relevant in the laboratory, whether in cells, in a test tube or in an animal model of the disease. Then drug candidates have to be created—perhaps small synthetic molecules or entire proteins—and screened to determine which of them can enter the body and the bloodstream and the relevant tissues and penetrate the cell in question, reaching the target and altering its function in some way that impedes the disease. This molecule has to be optimized for maximum efficacy with a minimum of side effects: it has to be tested for toxicity and perhaps reengineered; tested in live animals for safety; and finally, tested in humans—in perhaps thousands of patients—first for safety and then for efficacy.

There are many tight spots along this pipeline—and biotech firms are employing a host of new tools to open them up *(see "A Few Other Pipe Cleaners," p. 66)*. But the rate of attrition is still staggering. For every drug that makes it to market, 50 or 60 candidates will have failed. And that's in the pre-genome world, where the great majority of drugs are aimed at variations on those 500 familiar targets and based on well-known biological themes. With thousands of new drug targets, thanks to the Human Genome Project and other genomics efforts, it's a whole new ball game—one with extraordinary new promise, and an entirely new set of risks. The upside, according to a study by the investment bankers at Lehman Brothers and the management consultants at McKinsey, will be pharmaceutical advances so profound that they "are nearly impossible to imagine, let alone predict." The downside, says the analysis, could include a fourfold increase in the rate of attrition in drug development—200 drug candidates falling by the wayside for every single drug that makes it to market—and an astronomical rise in research costs. The report's stunning conclusion: in the short term, the flood of new drug targets could be fatal to pharmaceutical companies. Over the next five years, the report warns, "the industry could go bankrupt by trying to innovate."

The problem is that the sequenced genomes provide too many potential targets, but not enough biological understanding to go with them, a situation often referred to as "drinking from the fire hydrant." With so many targets, entirely too many would-be drugs could be rammed down the pipeline and make it to human trials, only to fail after enormous expense. Understanding the functions of genes in order to identify the most promising drug targets is proving to be one of the best ways to help unclog the drug development pipeline.

Frozen rodents: Lexicon's Arthur Sands says these cells, which can develop into "knock-out" mice, hold clues for drug discovery.

PHOTOGRAPH BY WYATT MCSPADDEN

Enter a host of functional-genomics firms that share a simple strategy: learn as much biology about these potential targets as technologically possible, and do it as quickly as possible. Of the many technologies used to those ends, says geneticist David Altshuler of the Whitehead Institute for Biomedical Research in Cambridge, MA, the most promising are those, like Lexicon's mice, that will allow researchers to directly manipulate the functions of all of an organism's genes one by one—and thus pinpoint those that play the salient roles in the causation, progression or prevention of disease.

A LEXICON FOR BIOLOGY

Before Lexicon came along, researchers had developed two techniques for creating knock-out mice, but both had severe limitations, explains Oliver Smithies, a pioneer of gene-targeting technology at the University of North Carolina at Chapel Hill. On one hand, researchers could target and disable a specific gene whose sequence was already known, but that process, as Smithies says, is "quite laborious, because you can only do one gene at a time." On the other hand, genes could be mutated at random, which can be done quickly and with relative ease; but then the researchers wouldn't know which gene had been mutated until they grew the animals to maturity—and perhaps not even then, if the absence of the gene was particularly subtle in its effect.

Lexicon's advance is a technique that mutates genes at random but does so by using a virus to insert a known sequence of DNA into the genes. That sequence not only disables the mutated gene, creating the knock-out, but remains behind as a signpost to identify precisely which gene has been put out of action. With this technology, says Sands, Lexicon has managed to knock out 40 percent of the genes in the mouse genome, considerably more than all the other mouse researchers in the world have achieved in the last decade. Pharmaceutical and biotech companies, and even academic researchers, can sign on with Lexicon to access this extensive mouse library, which Millennium Pharmaceuticals, Bristol-Myers Squibb, Johnson and Johnson and a half-dozen others have already done.

Because the knock-out mice are meaningless without diagnostic technology to pinpoint the effects of the absent genes, Lexicon's mouse facility in the Woodlands will house, not just 300,000 genetically compromised mice, but what Sands calls a "Mayo Clinic for mice" as well. This new center—where, of course, mice will be experimental subjects, not patients—will include a comprehensive radiology department, complete with MRI machines and CAT scanners designed to image the bones, organs and tissues of mice. It will have an immunology group to dissect rodent immune systems, and a neuroscience group, complete with a battery of behavioral tests, to study how the missing genes might affect brain development and behavior. It will have a developmental-biology group that will study how the absence of genes affects the development of the mice in utero, and a cardiology group, to look at how the absence of genes affects cholesterol, blood pressure, and heart and artery function. "Every medical department at Lexicon," says Sands, "will be geared to study the function of genes in live animals and find those that are the most valuable for drug discovery."

BIOLOGY ON THE FLY

What Lexicon is attempting to achieve with mice, a South San Francisco company called Exelixis is trying to do with fruit flies, worms and fish. These organisms have also established themselves over the years as workhorses in genetics labs, but Exelixis's innovation was to put them to work on an industrial scale in order to elucidate the functions of genes and identify promising drug targets. As the Whitehead's Altshuler puts it, "Flies and worms may not get diabetes, for instance, but they do sugar metabolism, and they do it pretty damn similarly to the way we do it. So you can find all the genes that affect sugar metabolism in the fly, find out if they're relevant to humans, figure out their function and do drug discovery."

Exelixis was founded by a trio of fruit-fly geneticists hoping to leverage the evolutionary conservation of genes and cellular circuitry that underlies these similarities—not to mention the arsenal of genetic tools honed by the decades of geneticists who have worked on flies, worms and fish. Since these organisms mature in just days or weeks, "You can rewrite their genetic code very quickly, so you can ask all the appropriate questions very quickly," says Exelixis chief scientific officer Geoffrey Duyk. At Exelixis, those inquiries usually start with flies, and so Exelixis has amassed a collection of knock-outs covering most of the 13,000 or 14,000 genes of the fly genome. Using that library, for example, Exelixis researchers are investigating angiogenesis, the process by which new blood vessels are formed. This is one of the hottest areas of cancer research, because a tumor will spur the growth of

A Few Other Pipe Cleaners

TOOL	PURPOSE	COMPANIES
DNA chips	Analyze the action of tens of thousands of genes simultaneously	Affymetrix, Agilent Technologies, Corning, Hyseq, Incyte Genomics, Motorola
Combinatorial chemistry	Generate and test hundreds of thousands of potential drugs at one time	Albany Molecular Research, ArQule, Pharmacopeia, Vertex Pharmaceuticals
Monoclonal antibodies	Attack disease with much less risk and shorter lead time	Abgenix, IDEC Pharmaceuticals, Medarex, Protein Design Labs
Predictive biology	Perform experiments on computers, rather than in cells or on animals	Entelos, Physiome Sciences
Protein analysis	Bypass the genes and go straight to the proteins and the pathways	Ciphergen Biosystems, CuraGen, Genomic Solutions, Large Scale Biology, Myriad Genetics

Shelf life: Exelixis's Geoffrey Duyk hopes tiny flies like those living in the vials on these racks will help elucidate genes' functions.

PHOTOGRAPH BY ANNE HAMERSKY

A window on the cell: Paul Negulescu and his colleagues at Aurora Biosciences use cells like those projected on the wall to study genes and screen drugs.

PHOTOGRAPH BY AMANDA FRIEDMAN

blood vessels to feed its proliferating cells. Find a way turn off angiogenesis, the argument goes, and you can choke off the cancer. Fruit flies could help researchers tease apart the genetic underpinnings of angiogenesis, even though they don't have blood vessels. What flies do have is a trachea: a system of branching vessels that carry air through the body. The development of the trachea is controlled by a process known as branching morphogenesis, which turns out to be the same process that creates blood vessels in humans.

The Exelixis researchers started studying branching morphogenesis in flies a year ago and expect to identify as many as 200 genes crucial to the process—all potential drug targets. The next step is to take these genes, find their counterparts in zebra fish, and then knock them out of the fish to see which are, indeed, involved in creating and maintaining blood vessels. Unlike flies, zebra fish do develop vasculature systems, just like mice and humans. And unlike mice and humans, zebra fish are, well, fish: their eggs develop outside the mother, and within 24 hours the body plan and all the organs are not only formed but visible, because the embryos and even the adult zebra fish are translucent. "You can follow in real time the development of the vasculature system in the embryo just by looking through a microscope," says Felix Karim, who runs the Exelixis angiogenesis program.

The research to elucidate exactly what these genes do and how they cause disease then proceeds by a process Karim describes as "ping-ponging" between studying the genes of interest, or their absence, in flies, worms, zebra fish, mice and even humans—all done in parallel for maximum speed. The entire discovery process, from fruit fly to validation of a promising target, might take only a couple of months.

The same approach can also be used to identify the genetic targets of existing drugs or promising compounds, which is what Exelixis is now doing for Pharmacia, Bayer, Bristol-Myers Squibb and the National Cancer Institute. "Once we identify the molecular target," says Duyk, "we can develop alternative compounds with the same target but which may have more optimal therapeutic and pharmacological properties."

CELLULAR INSIGHT

A still faster method for finding good drug targets, and even beginning to test potential drugs, forgoes model organisms and heads directly for the cells themselves. The technology is known as "cellular phenotyping," where "phenotype" is the genetic lingo for how a particular gene manifests itself in an organism—from blue eyes, for instance, to a propensity for certain cancers. In a cell, those traits might translate into the presence or absence of a particular pigment or a tendency toward irregular size and shape. Because vast numbers of cells can be grown quickly and tested in parallel, cellular phenotyping not only speeds the process of elucidating a gene's function, it opens the possibility of testing thousands or millions of potential drugs aimed at a particular target all at once. "You have to query the cell," says Brent Stockwell, a chemist at the Whitehead Institute. "Ideally, you would start with diseased cells and then look for chemicals that would simply convert them back to normal cells."

At Aurora Biosciences in San Diego, CA, for instance, researchers have created methods to measure in living cells the performance of the primary types of proteins that are known to be defective in diseases—and their accompanying cellular circuitry. Proteins called ion channels, for example, carry charged molecules back and forth across the membranes that surround cells and play key roles in maladies ranging from heart disease to diabetes to depression. That makes ion channels prime drug targets, but they are difficult to study because they only work when they're actually embedded in the membranes of living cells.

Aurora's technology to measure ion channel function uses a pair of fluorescent dyes that can be poured onto human cells growing in culture and then affix themselves to the cell membrane, one on the outside and one on the inside. Once attached, explains Paul Negulescu, senior vice president of discovery biology at Aurora, the dyes will respond to changes in the electric field across the cell membrane, which are controlled by ion channels. If the channels are conducting ions as they should be, then one of the dyes will glow. If they aren't, then the other dye will turn on. To study a particular ion channel that might make a good drug target in treating a particular disease, says Negulescu, Aurora researchers can genetically engineer test cells to produce that channel, or in some cases work with cells that mimic the disease. They use an automated process to put the cells into thousands of separate wells on an "assay plate" and add the dyes; they can then test thousands of potential drugs per plate, perhaps 100,000 a day, looking for the ones that modulate the channel in a way that might cure the disease with a minimum of side effects.

ULTIMATELY, THE STORY OF THE PHARMACEUTICAL INDUSTRY IN THE POSTGENOMICS MARKETPLACE COULD BE A SIMPLE ONE: THE COMPANIES THAT ARE THE MOST SUCCESSFUL AT ACQUIRING BIOLOGICAL INFORMATION—AND DOING SO QUICKLY—WILL BE THE ONES THAT SURVIVE.

Since Aurora first developed the technology, many of the major pharmaceutical companies have either licensed it or hired Aurora to develop custom variations of it. Aurora has also formed a consortium with Bristol-Myers Squibb, Merck, Pfizer and the Parke-Davis division of Warner Lambert to develop the technology further. In July, Vertex Pharmaceuticals acquired Aurora for about $600 million, in the hopes cell phenotyping will help bring more novel drugs into the pipeline and, says Vertex CEO Joshua Boger, help to more quickly unravel the biological workings of drug candidates already in development.

Ultimately, the more biological information pharmaceutical companies can acquire—and the faster they can acquire it—the more likely it is they'll survive in the postgenomics world. "At the end of the day," says biotech pioneer David Goeddel, who helped develop some of the industry's first drugs, "those that have the best understanding of the biology are going to have the best success getting drugs out." TR

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BIOTECH
BEYOND THE
GENOME

CONSULTING BIOTECH'S ORACLE

THE CEO OF HUMAN GENOME SCIENCES, BILL HASELTINE, HAS CREATED A POWERFUL NEW TOOL THAT HE JUST *KNOWS* WILL REVOLUTIONIZE THE DISCOVERY OF NEW MEDICINES. BY JON COHEN | PHOTOGRAPHS BY DAVID BARRY

Sitting in the conference room of Human Genome Sciences on a Friday the 13th, Bill Haseltine has a grin stuck on his face that says, today is a lucky day. It is the smug grin of a boy showing off an incredibly cool and impossible-to-find new toy. And make no mistake, the CEO of Human Genome Sciences has an incredibly cool new contraption at his fingertips. He also has a visitor whom he would love to impress: AIDS researcher Anthony Fauci, director of one of the most influential branches of the National Institutes of Health.

Haseltine's toy is actually one of biotech's most comprehensive databases. By merging a crack team of molecular biologists with computer jocks, the company has generated over the past eight years a user-friendly database of human genes and the proteins they code for that—Haseltine asserts—contains more clues about how to treat and cure disease than all other related databases around the world, commercial and public, put together. It's just the sort of outlandish boasting that has made Haseltine (pronounced "hazzle-teen") one of biotech's most controversial figures. But backing up his claim, the Rockville, MD, company already has moved five drugs into human trials, more than any other genomics-based biotech company.

"Tony, the feeling we have here is we're doing what most of the world will be doing in 10 years," says Haseltine, who at the age of 57 has slicked-back, thinning hair and wears owlish glasses. He then looks across the wide conference table that separates him from Fauci, pausing for effect, and says, "Maybe"—as in, maybe the clueless establishment will figure it out by then. Haseltine, who in his double-breasted suit looks more like a Wall Street moneyman than a former Harvard biology professor, follows this jab with a goose-honk laugh and rocks in his leather-lined chair.

Fauci is here to explore one of the potential gold nuggets found by Human Genome Sciences, a protein that stimulates antibody production. But while he's visiting, Haseltine agrees to let him ask the database—which Haseltine has nicknamed the Oracle—any question that suits his fancy. Fauci says he'd like to search for the "elusive CD8 factor."

Since 1986, AIDS researchers have known that HIV-infected people who defy the odds and suffer no immune damage spit out a mysterious chemical "factor" from a specific type of white blood cell dubbed CD8. Try as they might, AIDS researchers have failed to isolate this factor. "If we can't get the factor out of this, we can't get it," says Haseltine, as a coworker with a laptop begins to search the Oracle for all proteins produced by CD8 cells.

A projector hooked to the laptop shines its display onto a screen for all to see. The Oracle reveals that so far Human Genome Sciences has found 64 different proteins secreted by CD8 cells. At the time of Fauci's visit, a whopping 59 of these proteins had never been described in the medical literature or in any public database containing genetic and protein information on humans.

Fauci is beside himself. "That's terrific. It's amazing. It's breathtaking," he says. "I'm serious. There it is. This is fantastic."

TEMPLE OF GENES

For three days, I watched visiting scientists drop their jaws to the floor as Haseltine and crew put on similar shows. The idea that everyone but Human Genome Sciences is panning the wrong river for genetic gold is a story that Haseltine shops expertly. It is a story that portrays the company as miles ahead of the many biotech and pharmaceutical firms that similarly are trying to make money from genes. Haseltine, both brilliant and brazen, is of course the hero, and there is an entire cast of antiheroes. The story ends with wondrous new drugs coming to market at lightning speed.

And it's a story that many investors are buying: his company's stock, of which he owns more than three million shares (after cashing in $56 million worth this spring), traded for between $35 and $107 in the past year. If Haseltine overinflates the tale, well, only one letter distinguishes hope from hype.

The other side of the story begins with the Human Genome Project, an international $3 billion effort largely funded by the U.S. government. In 1990, the project organized academics around the world to decode the entire sequence of human DNA. Separate from that project, Human Genome Sciences became one of dozens of biotech companies that sprung up in the early 1990s with their own fleets of machines working 24/7 to scour the raw sequences of *A*s, *C*s, *T*s and *G*s—the abbreviations used to designate the four chemical building blocks of a DNA molecule—for genes. All were racing to patent as many genes as possible before the data would go public.

Shortly after he cofounded Human Genome Sciences in 1992, Haseltine left Boston's Dana-Farber Cancer Institute and tenure at Harvard University to become CEO of the new company. Within months of hanging up his lab coat, he signed a landmark $125 million deal with SmithKline Beecham (now GlaxoSmithKline) that gave the pharmaceutical giant exclusive rights to search the Oracle for leads on "small-molecule" drugs—the kind of pills that people swallow. Human Genome Sciences, however, retained the rights to develop treatments based on proteins—larger molecules, like insulin for diabetes or erythropoetin for anemia, that have to be injected. The deal blew minds in the biotech industry, which until then attracted investors based on the promise of bringing a drug to market, a process that could take over a decade and burn hundreds of millions of dollars. Human Genome Sciences showed that genomics companies could enjoy a steady revenue stream by selling information.

This bold move set off a cascade of events that changed what it meant to be a biotech company. Incyte Genomics, a Palo Alto, CA-based firm that sequences DNA, soon began selling access to its data and declared that it had no intention of even making treatments. Millennium Pharmaceuticals in Cambridge, MA, and Genset in Paris, France, soon cut multimillion-dollar deals of their own to help pharmaceutical companies find drugs by hunting through populations for disease genes. Next, a whole series of biotech firms sprung up around the idea of helping companies figure out the functions of genes, or the different proteins each gene instructs the body to make *(see "The Proteomics Payoff," p. 54)*. "If all we did was be a catalyst for this change, which we already have done, we'd be a success," says Haseltine.

Compared with other biotech startups, Human Genome Sciences had an inside edge as a result of its unusual relationship with a nonprofit outfit headed by J. Craig Venter. Venter left the National Institutes of Health because it refused to back a shortcut he had developed to sequence the genome, and in 1992 he signed a deal to join Haseltine in an elaborate business venture. Venter headed up the new Institute for Genomic Research, which sequenced DNA, while Haseltine ran for-profit Human Genome Sciences, which bought the institute's data and marketed it to pharmaceutical companies.

However, the two men's goals were as ill matched as their personalities. Venter wanted to publish data that Haseltine believed was proprietary. And soon Haseltine thought better of spending $10 million a year buying data from Venter's firm; Human Genome Sciences, he decided, could set up its own in-house sequencing shop and do the job more cheaply. In 1997, Venter and Haseltine formally severed their business ties. To this day, the men continue to engage in what Haseltine's sister Florence, herself an official at the National Institutes of Health, refers to as a "pissing match between alligators."

While Venter went on to cofound Celera—a company that, in June 2000, at the same time as the Human Genome Project, completed its own draft of the sequence—Haseltine became an outspoken critic of these massive sequencing efforts. Indeed, he has taken a view contrary to much of the conventional wisdom surrounding the Human Genome Project, including the growing consensus that humans may only have 30,000 to 40,000 genes—not the 100,000 that most scientists had previously predicted.

Haseltine, true to form, insists that a serious case of groupthink plagues the field. He still maintains that humans have at least 100,000 genes and might even have as many as 120,000. Haseltine knows this because, he claims, his company already has 90,000 distinct genes frozen away. "Why did they miss these?" Haseltine asks. "Because they decided genes have to have some similarity to known genes." And the majority of the genes Human Genome Sciences has in its freezers, he says, "have virtually no similarity to anything found before."

Human Genome Sciences has not published evidence to support these controversial claims, but the multitude and variety of whirring machines that continuously feed data into the Oracle make it difficult to dismiss Haseltine out of hand. His company has spent the last eight years sequencing genes, intensively studying the proteins they code for and simultaneously identifying potential drugs; other firms tend to have much more circumscribed goals. So Haseltine's real redemption will come if he fulfills his promise to use the database to turn out actual, lifesaving drugs. His company is focusing on the 10,000 genes that it knows code for proteins found on the outsides of cells, so-called secretory proteins that include hormones, receptors, immune-system messengers and enzymes.

HASELTINE'S REAL REDEMPTION WILL COME IF HE FULFILLS HIS PROMISE TO USE HIS DATABASE TO TURN RAW GENE INFORMATION INTO ACTUAL, LIFESAVING DRUGS.

So far, his company has moved five drugs into human trials that, if they work, may speed the healing of wounds, make cancer treatments less toxic, allow people with heart conditions to avoid bypass surgery, treat hepatitis C and spare the limbs of patients who otherwise would need amputations. By the end of the year, the company hopes to move at least three more new drugs into human clinical trials. And in July, the company reached the end of its commitment to provide GlaxoSmithKline access to the Oracle, creating even more exclusive opportunities for itself. "We are like kids in a candy store," says Haseltine.

Outside of GlaxoSmithKline and Amgen, the world's largest biotech company, no one else has yet used genomics to bring a drug into the clinic, says Haseltine. In his judgment, many scientists, in both industry and academia, simply don't understand how to mine the human genome for drugs, wasting time on regions of the genetic map that Haseltine has already dismissed as worthless. He says he has "a deep concern" about what the Human Genome Project will mean for people. "So far, it's a mixed blessing at best," he says. "The gene, for my purposes, is part of an anatomy…. Human Genome Sciences is going to redefine human anatomy. We're going to take it to a new level of resolution."

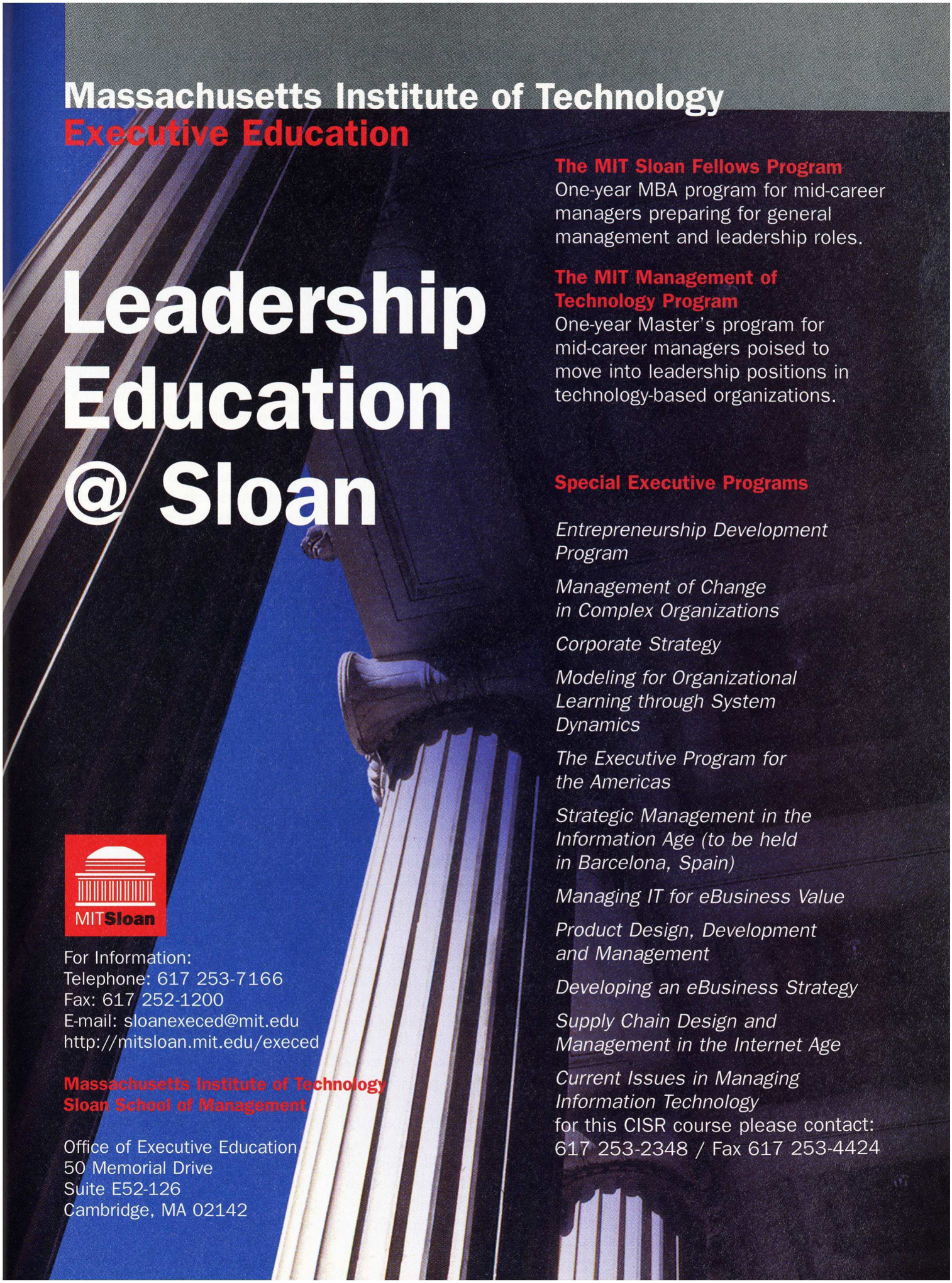
BARKING DOG

To appreciate why Haseltine has the audacity to pronounce that his company sees the light while others continue to grope in darkness, consider that Human Genome Sciences, like most young biotechnology companies, has no products on the market and, so, *must* sell its vision. It also helps to know a few things about William Alan Haseltine.

Haseltine and his three siblings grew up on a naval base in China Lake, CA, a "secret city" in the Mojave Desert where their father and other scientists designed the Sidewinder missile and the ejection seat used in fighter jets. Their mother, Jean, who taught French on the base, required frequent hospitalization for manic depression and a series of serious physical ailments, including severe psoriasis and a myopia that stressed her eyeballs and made her retinas detach. At seven, Bill, too, became ill with a heart condition called pericarditis that kept him out of school for six months.

"I did not like being sick, and I hated my mother being sick," he says. "I was terrified that she was going to die of blood poisoning. She had terrible psoriasis. I would actually go in and watch those red streaks go up her arm. And I knew if those red streaks went too far she would die. And that was a very upsetting thing. Kids are likely to feel responsible. It was a hopeless feeling." The turmoil led the young Haseltine to medicine. "I wanted to be a doctor to cure these diseases," he says.

After earning a BA in physical chemistry at the University of California, Berkeley, in 1966, Haseltine decided that his true love was research science, and he entered a PhD program at Harvard studying under Walter Gilbert *(see "Bankrolling the Future," p. 78)*. Gilbert, who shared the Nobel Prize in chemistry in 1980, remembers Bill as "a very lively student" who "alienated" some of the other grad students. Haseltine went on to do a postdoc-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toral fellowship at MIT in the lab of David Baltimore, who himself would win, in 1975, the Nobel Prize in medicine. "Bill was very smart and dominating," says Baltimore, who is now the president of Caltech. "He did some wonderful work, and he didn't make a lot of close friends. Bill is out to do as much as he possibly can in the world, and in some ways, it's good for the world, but it doesn't make him a beloved figure."

Haseltine moved on to Dana-Farber, which is affiliated with Harvard Medical School, rising through the academic ranks to become a full professor. He accumulated a résumé that also includes starting several biotechs, raising two children, becoming a big-shot AIDS researcher who hobnobbed with the likes of Liz Taylor, getting divorced, and marrying Gale Hayman, cofounder of Giorgio in Beverly Hills, CA, inspiration for Judith Krantz's *Scruples* and author herself of *How Do I Look? The Complete Guide to Inner and Outer Beauty: From Cosmetics to Confidence*. Along the way, Haseltine impressed colleagues with his polymathic, capacious mind and simultaneously irritated them with what critics like Leroy Hood *(see "Under Biology's Hood," TR September 2001)*, a leading figure in the biological research community, call his "arrogance and infinite selfishness." As Hood, who recently founded the Institute for Systems Biology in Seattle, puts it, "Bill raises as much animosity as admiration."

When I visited, Haseltine's office at Human Genome Sciences offered another clue as to why he rubs so many scientists the wrong way. A table framed by a long wall of windows looking into the Maryland woods had on it little plastic-coated wire stands displaying a few dozen scientific journals, books and popular magazines. The collection was, in its intellectual sweep, mesmerizing. But for all that gravitas, the display was obviously there for show—who puts what they're reading on little stands?—and was meant to dazzle the visitor. Haseltine's words, similarly, often aim to dazzle, which is antithetical to the belief of many scientists that data should speak for themselves.

Sitting in his office, I ask Haseltine about his legion of critics, and he smiles. "The dog barks and the caravan passes," he says in French. Then, in English, he adds, "Who gives a good goddamn what people think? Do well and let them say what they want."

There is substance behind Haseltine's bravado, which is obvious to anyone who sees a demonstration of the Oracle—something that, remarkably, few leaders of the genomics revolution have done. "They have a very arrogant, self-centered view, which is they are the world, they are the heroes, they are the white knights," says Haseltine. "I don't think that people have any idea of the power of what it is that we do, because it's two or three steps beyond what they can imagine."

The back wall of the company's conference room explains another reason that relatively few of the world's scientists have had access to the Oracle. The wall is cluttered with dozens of bronzed versions of official documents from the U.S. Patent and Trademark Office. In fact, by July of this year, Human Genome Sciences had 179 "gene-based" patents and had filed patent applications on at least 7,500 other newly discovered genes for which it has declared medical utility. Anyone who wants to use the firm's database must agree to give up any medical utility discovered. So researchers stay away.

"THE DOG BARKS AND THE CARAVAN PASSES," HASELTINE SAYS IN FRENCH. THEN, IN ENGLISH, HE ADDS, "WHO GIVES A GOOD GODDAMN WHAT PEOPLE THINK?"

THE ANSWER

One morning, I observe a meeting with scientists from a biotech company that might form a joint venture with Human Genome Sciences. Haseltine takes them on an Oracle tour. "We have more answers than you have questions," he says at the outset.

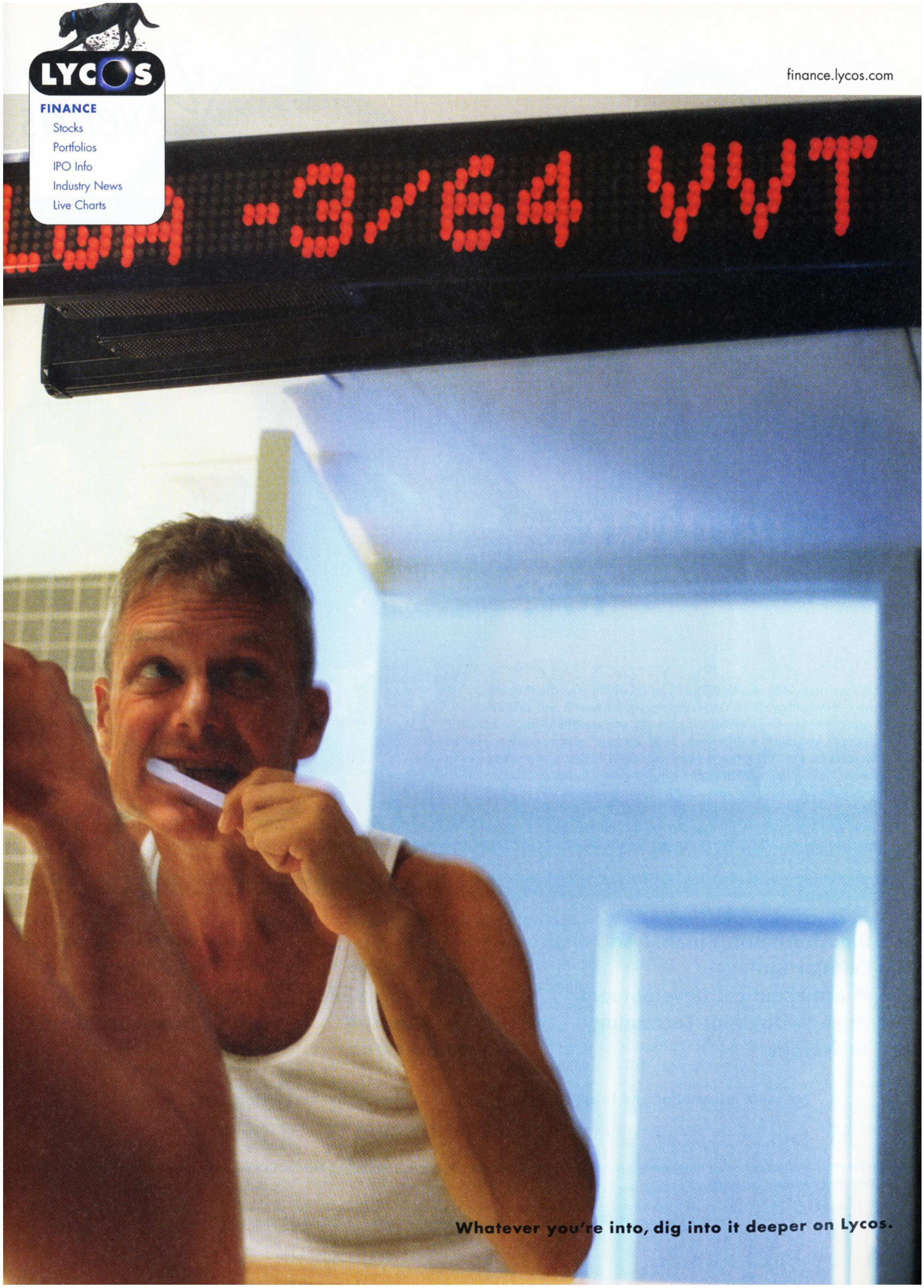
As much bluster as Bill Haseltine pumps out, as combative and grating and self-serving as he may be, his company's database speaks for itself. Haseltine begins scrolling through the endless DNA samples in the Oracle. He can look at a particular gene and see how it's expressed in a six-week-old embryo compared to, say, an embryo that is nine weeks old. Likewise, he can compare the genes expressed in a fetal kidney with those from an adult's, a healthy ovary to one riddled with cancer. He randomly selects a gene, jumps to a public database run by the National Institutes of Health, and finds a similar gene present in worms. Another click of the computer shows that the protein is secreted. Human Genome Sciences has done 69 different biological tests with the protein, looking at how it relates to everything from myeloid leukemia to immune-system cells. A diagram even shows the biological pathway within which the protein operates. "We've already patented it," says Haseltine.

Haseltine decides to look at levels of the protein in an adult kidney. His company has found 583 genes that are expressed in kidneys, a full 363 of which have not been described in public databases. Of these, 52 code for secreted proteins, and 27 of those Human Genome Sciences has filed patents on. Haseltine decides to swing the Oracle in another direction and look for the most abundant gene in this kidney sample. It's septin. "Who knows what septin is?" he asks. "Not me. We're about to find out." Septin turns out to be involved with blood clotting.

What does all of this mean to the discovery of new medicines? It is plain that Human Genome Sciences has built a jazzy new type of microscope that, as Haseltine says, offers a view of human anatomy that we've never had before. What is much less clear is when this knowledge will help humans lead longer, healthier lives.

Francis Collins, the researcher who heads the Human Genome Project for the National Institutes of Health, says scientists have to strive not to oversell the promise of genomics. "I have no doubt that in 50 years, much of medicine will look entirely different, and much of that will be because of genomics," he says. "It's a revolution unlike almost any other that's happened since the discovery of antibiotics. But we have to be honest with the press and the public and ourselves that the timeline is longer than we wish."

Haseltine, in contrast, hears the wheels of a caravan turning and the faint sound of dogs barking in the distance. TR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Q & A

Bankrolling the Future

Ethernet inventor Bob Metcalfe and Nobelist Walter Gilbert, now both venture capitalists, meet to pick the most significant emerging technologies in IT and biotech. PHOTOGRAPHS BY JOHN SOARES

Earlier this year an intriguing coincidence took place in the world of innovation: at almost the same time, Bob Metcalfe and Walter Gilbert decided to become venture capitalists in the Boston area. Both Metcalfe and Gilbert are distinguished innovators who have played many different roles in the process of bringing research to market. Metcalfe invented the Ethernet and founded 3Com to commercialize it. After leaving 3Com, he went on to a career in publishing and punditry. Gilbert has had a brilliant research career in molecular biology, sharing the 1980 Nobel Prize in chemistry for discovering a fundamental method for sequencing DNA. He cofounded one of the very first biotech companies, Biogen, in 1978 and has also had a hand in starting several other biology-based companies, including Myriad Genetics.

Now both men are approaching the world of entrepreneurship and innovation from a new angle. Metcalfe has stopped writing his column in *InfoWorld* and joined Polaris Venture Partners of Waltham, MA. Gilbert has taken a leave of absence from Harvard University to join BioVentures Investors, in Cambridge, MA. In spite of the parallels between their careers, Metcalfe and Gilbert come from different worlds—information technology and biotechnology—and had never met. *Technology Review* thought it would be interesting to bring them together to talk about the current climate for investment, the most important emerging technologies and why they became venture capitalists now. Editor in chief John Benditt mediated a conversation over dinner in downtown Boston.

Table talk: Benditt (center), Metcalfe (middle left) and Gilbert (middle right).

TR: How is venture capital activity different from when you started out forming new technology-based companies?
GILBERT: Back in the 1970s, venture capital groups were trying to find a few engineers or a few scientists to put them together with business people and form a company. There's very little of that now. To do that takes great effort, constant nurturing, and there's only a small amount of money involved at that stage. So if one runs a very large fund, one can't afford to put capital into small "seed" efforts like that because that would spread the money into too many companies. Nowadays, when a venture capital group supports the growth of a small company it is generally in the second, third or fourth round, with large investments, as opposed to the very beginning.

TR: How has the broader picture changed since you founded Biogen?
GILBERT: We have shifted from a period in which people doing biology had an ivory-tower view of the world, in which there were no practical applications for what they did, to a view in which everything appears against the background of immediate practical application. Back then, it was like breaking your oath, breaking the code of purity, to think about founding a company. There are thousands of biotechnology companies now; there were none then.

TR: How was it possible for you to go beyond the idea of an "oath of purity" and get involved in founding a company?
GILBERT: That results from having a strong view of the public good and believing that molecular biology could actually make a useful pharmaceutical, so that it was worth spending my time to do that and to show that it could be done. At that time the rest of our community didn't think it was possible. I learned a lot about the world doing this that I didn't know before, and in some ways, serving Mammon is cleaner than not serving Mammon, because greed is a very simple motivator, and other motivators in science are much more complex.
METCALFE: But there is an ideology question floating around here. There are people who believe that making money is evil. They're wrong. But they believe it.

TR: Right. So how were the two of you able to get beyond those blinkers?
METCALFE: Well, if you want to see your ideas out in the world, what is the most powerful way of projecting them? Not through a nonprofit organization begging for donations. The best way to convey ideas, I think, is with the people who had the ideas. I don't think it works well for the academics to sit here and generate the new ideas and then write the papers and then have other people put them into practice. I learned that at the Xerox Corporation in the 1970s.

TR: What was your experience there?
METCALFE: Well, we had this model that there would be a research center, and then there would be this advanced academic development laboratory, and then there would be engineering departments, and there would be these products. So the guys in the science groups, where I was, kept throwing these ideas over the transom, and the guys on the other side either kept dropping them, or they were proud of their own work, so they would ignore everything we did and start over. But they would come up with what we considered to be dreck. So a few of us started migrating downstream, taking the ideas with us instead of trying to get them adopted by throwing them over the transom.

TR: The two of you have been both basic researchers and entrepreneurs. Now, in your role as venture capitalists, do you look for both those capabilities in one person?
GILBERT: We seldom look for that. It's too hard to find. A more typical pattern in a startup company is that one has a technical group, including the people who came up with the idea, and also someone else who's trying to push the business, worrying about the money-raising, creating the capital.

TR: What is the investment climate like now in venture capital?
METCALFE: A tremendous investment stream has been created to about five or six hundred venture capital firms, about three or four hundred of which are completely screwed up, and most of them are going to die. And the limited partners, the pension funds and so on, who provide the funding for the venture capital firms are saying, "Okay, we're going to invest in the two hundred firms that didn't screw up." But that can actually create a problem in that the limited partners want to give your firm more money than you can reasonably deal with right now.

TR: Some would say it's a funny time to become a venture capitalist. We've just been through this great big "new economy" bubble, and everybody's feeling burned. So why did you two distinguished innovators decide to try it now?
METCALFE: It has to do more with my personal life cycle than with the state of the markets. I had finished my previous career as a journalist, and venture capital was the next thing. I like entrepreneurs and I like high tech. This is another way—as journalism was before—to stay with those topics and those people. Just another way. New and challenging things to learn but still pretty much involved with innovation.
GILBERT: Well, actually, this is a great time to be a venture capitalist. Valuations are low, so it's an excellent time to buy a company. Too many people think that if valuations are low, that means they're going to stay low in the future, as opposed to "valuations are low today, but the cycle will take us back up again." In my case, I've been very interested in small companies. I've founded a number of small

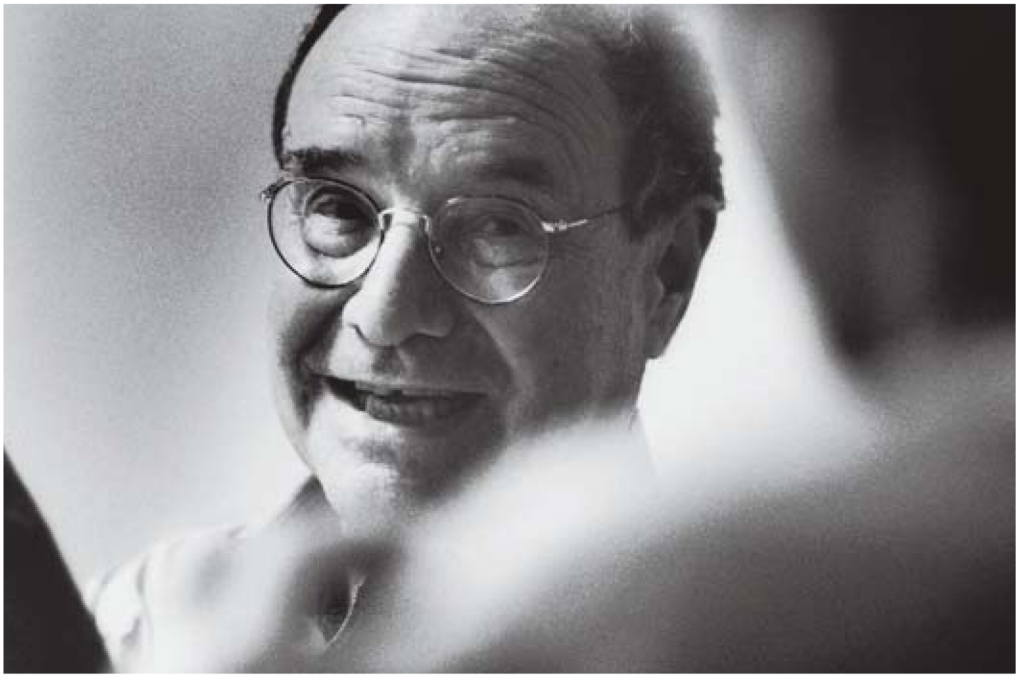
"This is a great time to be a venture capitalist. Too many people think that if valuations are low today, they're going to stay low in the future, as opposed to thinking, 'valuations are low today, but the cycle will take us back up again.'" —WALTER GILBERT

companies in recent years, and so I stepped back and said, "Well, maybe I shouldn't just ask for money, I should participate in the venture capital structures that give money to these companies."

METCALFE: I heard this from a man named Paul Deninger, who runs Broadview, which is a major mergers-and-acquisitions company, and his advice was, "Forget what happened over the last two years, because there's nothing to be learned from it."

TR: Nothing?

METCALFE: Nothing. It was just a crazy aberration, and if you try to learn something from it you will be misled and distracted. Delete it from your memory, because it was just such an extreme speculative bubble. The trouble is, there's now an army of zombies whose thoughts about how the world works were formed during this period. They're doomed, because for the rest of their lives, they will try to recreate that situation, which won't recur… at least for a long time. You see them occasionally when they come in, expecting a pre-money valuation of $175 million because there's nine of them and they're really charming.



TR: So the recent experiences don't inform what you're doing as venture capitalists? They don't change what you look for?

GILBERT: If you're serious as a venture capitalist, you try to look at the serious aspects of companies. Do they have real intellectual-property elements which they have protected that could be of commercial value? And if there is commercial value, what is the nature of that value? The dot-com cycle was a strange one, because people were interpreting the number of clicks on your Web site as income.

METCALFE: The basic idea of the bubble was, "We're going to give away what it is we do best and make money some other way, such as monetizing the eyeballs that we're able to attract." You see this with Linux, where they say, "We're going to give away our software, but we're going to make money some other way." The trouble was, those other ways never developed, in particular the anticipated advertising never materialized.

TR: Now I assume you [Metcalfe] are working mostly in information technology and you [Gilbert] mostly in biotechnology. What are the areas you think are most exciting these days?

METCALFE: I don't think those are two different categories. I think it's a continuum. This is an argument I have with my partners. The way my partners characterize our investments is that we're two-thirds info, one-third bio. But I'm a curious person. I love to learn. So I sit in on these biotech presentations. And the bio guys are talking about computers and bits and databases, and, of course, many of the computer guys are talking about applying biology to computing. So I think it's healthier to consider it a continuum, rather than this is info, this is bio.

GILBERT: It is a bit more confusing than that in biotech. There are several different types of companies. Obviously, one type of company is developing novel products, novel drugs. There's another whole field of companies developing novel technologies, which can help other companies develop products. Companies like Celera, for instance, which is sequencing the human genome. And then there's the whole field of bioinformatics, the issue of whether you can apply computers to biology. The amount of information you're trying to work with can only be dealt with by information technology, and the questions you ask can only be phrased in terms of computer programs and computer analysis.

TR: We've had a wave of genomics companies, and the next phase seems to be proteomics, companies trying to identify all the proteins in the human cell and the ways the proteins interact.

METCALFE: I'm involved in a company that's the next wave after that. There's genomics, and there's proteomics, and there's the next one after that. It's called glycomics, and I'm going on the board of a company that does that *(see "Glycomics," p. 33).*

TR: Tell us about it.

METCALFE: Well, the DNA creates the proteins within the cells, and then sugar molecules are added to the proteins. The sugars affect how the proteins behave. The alphabet of sugars is more complicated than the alphabet of proteins, which is more complicated than the alphabet of DNA. Please check me if I'm wrong.

GILBERT: Well, there's a slight exaggeration here. I don't want to disparage your company, but up till now the glycosylation patterns, the patterns of sugars attached to the proteins, has been a technology desperately seeking a useful target.

METCALFE: This came about because Bob Langer of MIT, who has done probably 10 or 15 deals with Polaris, comes in with two PhD guys who have done this glycomics work. So I asked whether it's possible that cancer cells attach their

sugars in a specific way. And they said, "Yes, in fact, we think we might be able to detect cancer way early by looking for these specific patterns of glycosylation," or attachment of the sugars to the proteins.

TR: Dr. Gilbert, is this also an area you've been looking into?
GILBERT: No, although given an opportunity I might invest in that company.

TR: Is this postgenomics?
GILBERT: Well, actually it's both pre- and postgenomics. Glycosylation has been around for a long time. And yet no one has yet shown that there is a real alphabet of glycosylation that could be deciphered as the genetic code of the DNA has been deciphered that would prove to have practical value in terms of how the proteins behave.

TR: What would you pick as upcoming significant technologies in your fields?
METCALFE: I am telling people the next big thing, the next big thing on the Internet, is video.

TR: Software to convey video over the Internet?
METCALFE: Well, the bandwidth. The content, the switching, the bandwidth, everything related to the delivery of video.
GILBERT: Perhaps. But there is still a major question of whether this might develop in a peer-to-peer fashion or as a broadcast medium, with a central source sending content out to large groups of viewers.
METCALFE: Yes, well, we had the same experience with earlier stages of the Internet. What you saw is that communication led and content followed. E-mail beat out weather and stock quotes. They came later. So the question you're asking is, will the initial killer apps of video be communication or content oriented? Will they be movies, or will they be videoconferencing or video telephony? And if there's a recapitulation, then you're absolutely right, the videophone will drive video rather than video-on-demand movies.

TR: Sure, but lots of people have said video on the Net was the next big thing. So why does your gut say that it will actually materialize now?
METCALFE: Well, in microprocessors, we went from one-bit to two-bit to four-bit to eight-bit to 16-bit to 32 to 64. Bill Gates got to be the wealthiest man on earth because he knew this progression would continue. And he made his money on the transition from eight to 16. A lot of people said, "Well, we're not really fully utilizing the eight-bit microprocessor, and there's no software for the 16-bit microprocessor, so it's ridiculous that anyone would bet on that." And Gates knew 16 was next and 32 was after that. Now, in the bandwidth world, the same thing is happening: one kilobit, 10 kilobits, 100 kilobits, 1,000 kilobits. It's sort of an obvious progression related to the unfoldings of bandwidth. The backbones

are now 10 gigabits, but it's going to 40 gigabits.
GILBERT: And what do you see as the underlying infrastructure?
METCALFE: I'm on the board of a public company called Avistar [Communications] that does desktop-enterprise videoconferencing. This dates back to before my involvement with Polaris.
GILBERT: Well, we're still waiting for good videoconferencing. We've been waiting for years, and there may not be good videoconferencing for another 20 years.
METCALFE: Well, this company is the next attempt. I'm watching them introduce new versions of their software with new features, and then we all watch with anticipation at the usage levels, measured in minutes per day and how many users there were and how long it takes to sell the new feature. The sales cycle is long because there are so many people walking around who have had their hearts broken in previous versions of videoconferencing.

TR: What else will be needed to make the video revolution go?
METCALFE: Well, there's a company I can't name but whose business plan is before Polaris. They make a chipset for editing HDTV. And there isn't a lot of HDTV around now.
GILBERT: Not a lot of broadcasting yet.
METCALFE: Yes, but we think that HDTV is the coming thing.
GILBERT: And your basis for thinking that?
METCALFE: The inexorability of progress and the fact that HDTV is gorgeous. More people will want it eventually. And it's not enough to have the TVs, and it's not enough just to have the broadcast facilities. You're going to need the editing facilities. Therefore you need these chips. The consensus among the partners is that we should probably do this investment, because these chips are going to be needed. My own attitude was triggered by the fact that my 12-year-old son gave me as a Father's Day gift a movie that he made using [Apple Computer's] iMovie on the Macintosh, with a digital camera, titles, music. So this is coming.

TR: Are the chips for professionals or consumers?
METCALFE: The initial plan is based on professionals. As the prices come down, this will become a widespread phenomenon; just as people write letters, they can make movies for grandma and send them over the Net.

TR: If your grand vision is correct, does it matter to you when it comes true?
GILBERT: It's very easy to pick things that will prove profitable. The question is, when? The entire issue is, can you invest in a way that produces a return very very soon?
METCALFE: Timing is everything.
GILBERT: Timing is everything. Timing is every element of the next strong investment.

TR: Dr. Gilbert, Bob Metcalfe has gone out on a limb and said video is the next big thing in IT. What do you think is the equivalent from within biology?
GILBERT: I don't think I know anything that's going to be as important as Bob thinks video is going to be. In biology now we have some very large fundamental problems that need to be solved, problems of basic scientific knowledge. We now have a very good view of the human genome. But we don't have good ways of understanding how many genes there are in the human genome or how many relevant proteins there are. That is, in fact, a bioinformatics problem, and it hasn't been solved.

TR: So one issue is understanding how many genes there are?
GILBERT: We can't do that yet in a totally convincing way. I would think we would be able to within a few years. And I think we will in fact also work out the two next major problems in biology. One is the problem of how proteins fold up into their specific three-dimensional shapes—how to predict that from their DNA sequence. And the other problem is deciphering the program of how the egg develops into the complete organism.

TR: And are those problems being solved by the companies you invest it?
GILBERT: The scale of these problems is beyond the reach of the average small company. They're very large problems. And if they're solved, then it's difficult to sell the result. Is it useful for a company to try to solve the protein-folding problem? In some ways it's questionable. It's very hard as a company to sell that as a useful approach. There are companies trying to do that. Would I invest in them? Probably not.
METCALFE: Well, I'm involved with a company that uses peer-to-peer software for doing protein folding. And it seems to me that there is a way to make this kind of work profitable. Couldn't you just run through the human genome, which has now been catalogued, and fold every protein, and create another database of the foldings of every protein implied by the genome?
GILBERT: You could in principle, but you can't in practice, because you can't do the calculation.
METCALFE: Well, let's assume that in the fullness of time, they will solve the problem, so now we have a complete database that is not the human genome, but it's all the expressed proteins of all the genes of the human genome. What could you do with that?
GILBERT: Well, you could sell it to somebody. But can you sell it for enough to have made the whole thing worth doing? It's like with Celera. Are the companies they sell their DNA sequences to going to offer enough to make the half-billion dollars in Celera's costs to do the genome worthwhile? Are they actually going to get enough income to match that? I don't think so.

TR: So those problems will be solved in the universities or by government funding?
GILBERT: Well, the big problems, the fundamental problems, get solved in the university. And we need the government-funded projects for things that are far out. Celera would never have been able to sequence the human genome without a massive initial public investment.

TR: So does that mean we have to wait until these huge problems are solved to get a return in biotech?
GILBERT: No, not at all. The individual drugs will be profitable, not the whole database of information. In many areas we can already find specific molecules that will have important effects. I mean, the exciting subfields are things like neurobiology—can one enhance memory? I'm involved in a company trying to enhance memory, so I think that's a perfect example. With Eric Kandel of Columbia University I helped to found a company called Memory Pharmaceuticals.

TR: What is the company doing?
GILBERT: They develop small molecules to use as drugs that affect memory. We already know enough about what goes on in the hippocampus [a brain structure that plays a central role in memory] to enhance the way that the cells talk to each other. And one can study the process of memory further by turning genes on and off in the hippocampus of mice. You can make dumb mice smart and vice versa by switching the right genes off and on.

"What happened over the last two years was just a crazy aberration, and if you try to learn something from it, you will be misled and distracted. Delete it from your memory, because it was just such an extreme speculative bubble, which won't recur...at least for a long time."—BOB METCALFE

TR: Well, thank you both very much for speaking with the readers of *TR*. One of the things that's most interesting to me in this conversation is that although you come from different backgrounds—in infotech and biotech—there is so much overlap in technologies these days that you may wind up in your new role as venture capitalists competing for the same companies.
GILBERT: Well, my general reaction to the discussion we had is that we may be potential coinvestors.
METCALFE: It's a win-win situation.

ENGINEERING ODYSSEYS

Finish your summer book list? Mine included *Ibn Battuta: Travels in Asia and Africa 1325-1354*, translated by H. A. R. Gibb; *The Voyage of the Beagle*, by Charles Darwin; and a pair of books by Boston's most enduring couple, Brad and Barbara Washburn (*The Accidental Adventurer: Memoir of the First Woman to Climb Mt. McKinley,* by Barbara with Lew Freedman; and *Exploring the Unknown: Historic Diaries of Bradford Washburn's Alaska/Yukon Expeditions,* edited by Lew Freedman).

The pattern is obvious. Burning with wanderlust, having O.D.ed on in-flight magazines, I've gone to the sources in search of a fix.

This may seem odd. For the last decade, I've schlepped around the world, visiting all 50 states, about half the world's countries and every continent but Antarctica. One might think I'd long for homey books by Bob Vila or Martha Stewart. Instead, I am following the footsteps of many other curiosity seekers. And since science is essentially a curiosity-seeking business, it isn't surprising that so many scientists have wandered out of the laboratory and into faraway places. The jarring experiences you get on an ambitious trip are a spur for new ideas. Many a creative work, whether in science or the arts, begins with a boondoggle.

Alexander Graham Bell was an early president of the National Geographic Society. Yale professor Hiram Bingham used to salivate over the blank spots in the map (there still were some in the 1920s). He could have been the real-life model of Indiana Jones: on one typical quest in 1911 into the jungles of Peru he stumbled upon the lost city of Machu Picchu. Nobel physicist Richard Feynman fixated on Tannu Tuva. Murray Gell-Mann, another Nobel physicist, seems to have been everywhere. Ask him about Bhutan. He may reply in Dzongka.

Darwin's five-year, round-the-world voyage on the *Beagle* is the sort of intellectual and geographical epic that scientific legends are made of. Three years into the journey, green and puking with seasickness nearly every day, he reached the Galápagos Islands, about 1,000 kilometers west of Ecuador. There he saw with his own eyes a startling pencil sketch of evolution in action. It blew his mind. But think about this: if Darwin hadn't gone, he most likely would have wound up as a career pastor. Charles Darwin: a *creationist*?

A friend of mine was an MIT student of strobe light inventor Doc Edgerton, who dragged him to the Bahamas and the Scottish highlands, ostensibly to try underwater gadgets in search of Atlantis and the Loch Ness monster. Now, I had assumed that Atlantis was on Santorini in Greece (site of the largest volcanic explosion known on earth), not the Bahamas, and that Nessie-spotting could only be done after a thorough tour of regional single malts. But on those trips, they debugged things like sonar, hydrophones and Doc's underwater cameras. Anyone who has taken a picture with a Nikonos owes a debt of gratitude to intrepid souls like Edgerton and his dive buddy Jacques Cousteau. Their cameras were worth far more than the sea monsters they never saw.

Scientists aren't the only ones with wanderlust. Johann Sebastian Bach crisscrossed Germany on foot: ambitious hikes for a man with a Sunday church job and a stable full of kids. Franz Liszt played concerts from Paris to Baghdad to Kiev; had he never written a note of music, he would have gone

MARTIN O'NEILL

down as one of history's great travelers. Leonard Bernstein was a travel agent's dream, a man who took his musical passions all over the globe. Think of Teddy Roosevelt, not just a president but a serious bushwhacker who almost single-handedly kept Willis and Geiger in the safari jacket business for decades. Or Ben Franklin, who pioneered shuttle diplomacy and earned frequent-sailor miles with his work in Paris.

Writers and storytellers are also impelled to travel. There was Hemingway. Or Mark Twain (did you know he took a four-month trip to Hawaii and wrote about it as a travel correspondent?). Or Michael Crichton, whose life has been a grand odyssey (his book *Travels* is a clue). I once checked in at the Galle Face hotel in Colombo, Sri Lanka, and noticed that filmmakers Sir David Lean and Steven Spielberg had signed the registry before me. So had Crichton. And Arthur C. Clarke. Coincidence?

While I was there, I recalled that the giant bats in *Indiana Jones and the Temple of Doom* were the same Sri Lankan bats Lean had used in *The Bridge on the River Kwai*. Sir David spent long fallow periods between films on journeys of his own. Movies like *Doctor Zhivago*, *Lawrence of Arabia*, and *A Passage to India* all share an interesting feature: a magnificent steam-driven train chugging through some exotic land. It is a symbol of epic lives.

So the travel bug infects us for good reason. And to think I thought when I joined the faculty at MIT that I'd be wiping the chalk off my coat. Ha! It soon became obvious why Media Laboratory faculty were among the world's most frequent fliers. Computers and networks spread digital technology everywhere, so even more than usual, MIT professors began receiving lecture requests from every corner of the globe. And it happened precisely when technology was turning the travel industry on its ear.

Suddenly you could book a whole trip with an e-mail or two. Paper tickets vanished into e-land. Behind the scenes, invisible travel databases swung into place. I used to amuse myself by bringing a tiny (and at the time, superadvanced) Global Positioning System device on planes. I watched the atlas on my laptop glide by, a little like being in a glass-bottom boat. My e-mail was stamped with a lat/lon to show where I was when I sent it. Then the airplanes began showing the same video maps. And the European guide *Relais and Chateaux* began listing GPS coordinates for each country inn.

Technology has made travel *so* easy that getting away is getting hard. Airports have morphed into a maze of indistinguishable shopping malls. Used to be you'd travel to go someplace different. But often when you arrive it feels like you never left. It's a strange trend. *Real* travel experiences seem to have succumbed to a kind of global Disneyfication. Blank spots have been scrubbed from the map. Journeys are canned and packaged. Wherever you go, TVs are tuned to CNN, Internet browsers are set to My Yahoo! and cell phones ring. Shopping malls sell the same Godiva. The traveler sails through a veneer of reality on a magic carpet of databases and global brands.

With effort it is still possible to get a taste of different realities. And young scientists still need to be trailblazers. They benefit from being led astray, into the unknown, once in a while. We all do.

One of MIT's great educational movements took place in 1969, when Edwin H. Land helped launch the UROP program, along with Margaret MacVicar, who really shepherded it into existence. UROP—which stands for Undergraduate Research Opportunities Program—gives students a chance to work side-by-side with great scientists on the most thrilling questions of all: questions nobody knows the answer to.

With MIT's endless industrial ties, labs extended readily through corporate arms. And now, as never before, the world is our laboratory. There are opportunities for young scientists to get way out of the box and do extraordinary things. My own undergraduates have been to Everest and Greenland for geology, to Singapore and Japan for infrastructure; they've taught English in rural China. This fall, several of them will attend the University of Cambridge, part of MIT's new exchange program, where they may finally learn English!

The jarring experiences you get on an ambitious trip are a spur for new ideas. Young scientists need to be trailblazers. They benefit from being led into the unknown once in a while.

In 1325, when Ibn Battuta left Marrakesh as a 20-year-old, he was on his *hajj*—the pilgrimage to Mecca that was (and still is) part of every Muslim's coming of age. It marked the end of one's schooling—and the start of an education. After reaching the holy city, he kept on going: he literally walked around the world for about 30 years. He saw a more fantastic spectrum of intensely different cultures than perhaps any other traveler before or since. His motto: "Never the same road twice."

That's the way of science, too.

In a world where the beaten path through the global village is so well paved that it takes work to get off it, I love getting advice from tireless Brad Washburn. Brad, a man who nowadays measures his age in geological epochs, and who might have dated Amelia Earhart (but was smart enough to land Barbara), founded Boston's Museum of Science and is one of the world's great explorers. He loves to recite his favorite line from Goethe: *Whatever you can do, or dream you can, begin it. Boldness has genius, power and magic in it.* TR

COURTESY OF TRANSRAPID INTERNATIONAL

MAGNETICALLY LEVITATED TRAINS

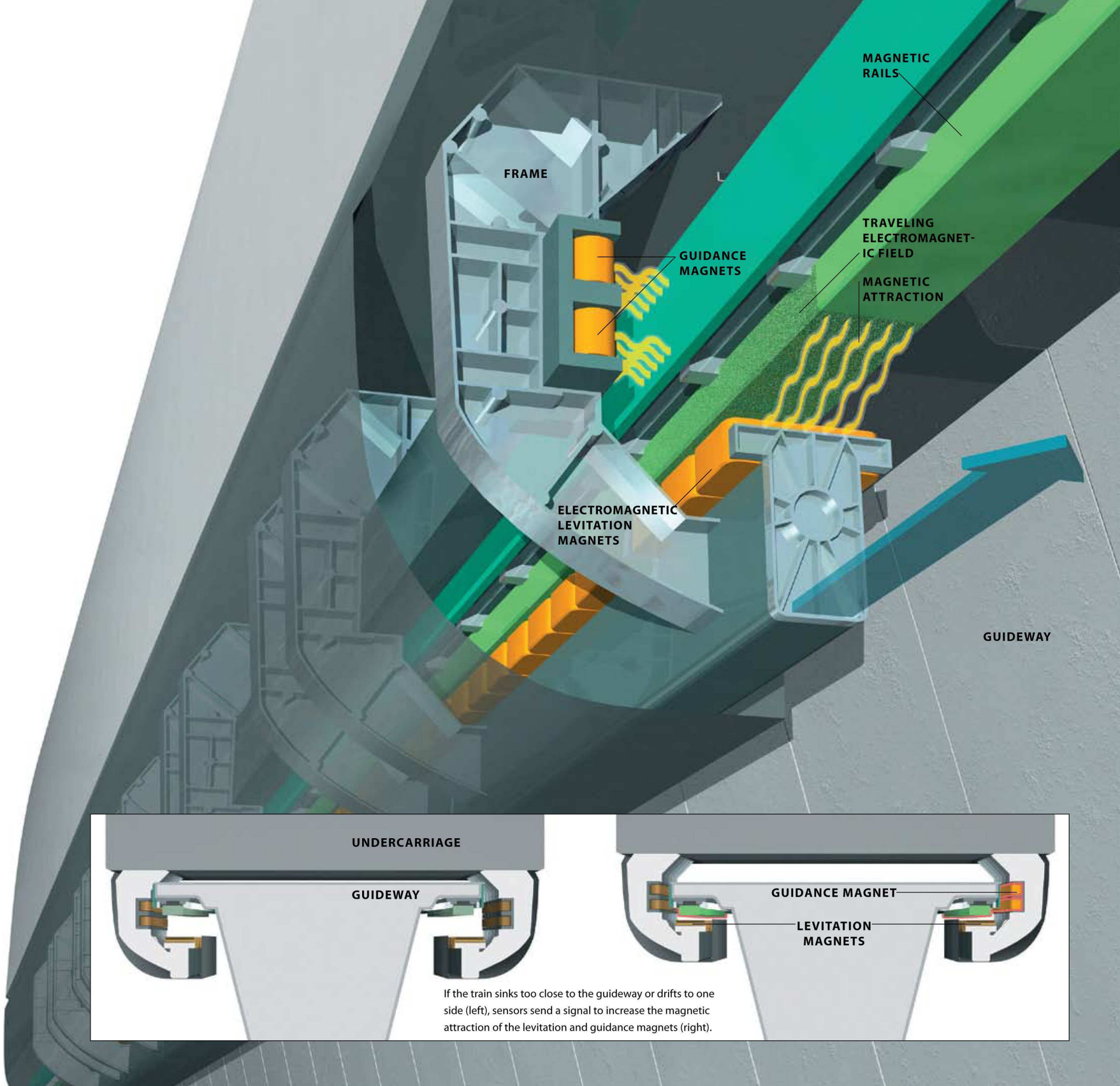
BY TRACY STAEDTER | ILLUSTRATION BY JOHN MACNEILL

The future of transportation may find travelers flying on vehicles that have no wings. Magnetically levitated trains, which use the attracting and repelling forces of magnets, jet through the air just millimeters off a specialized track—some at speeds of 550 kilometers per hour. Maglevs are quieter and consume less energy than trains with wheels that touch the track.

The city of Shanghai, China, is building a high-speed German maglev dubbed Transrapid, which will whisk people the 33 kilometers between downtown Shanghai and Pudong International Airport. And by 2004, the U.S. Department of Transportation will fund a $950 million project to build a maglev train either between Baltimore and Washington or between Pittsburgh International Airport and downtown Pittsburgh.

The Transrapid train is propelled, guided and levitated by magnetic forces. Frames attached to the bottom of the train curve down around a T-shaped guideway; electromagnetic levitation magnets attached to the frames are attracted upward to magnetic rails on the guideway's underside, lifting the train up about 15 centimeters. An alternating current passing through the guideway creates an electromagnetic field that travels down the rails. The magnets on the frames are attracted to this traveling field, which pulls the train forward in much the same way that a refrigerator magnet moved underneath paper pulls a second magnet across the top. To slow the train down, the traveling field is made to move in the reverse direction. Sensors monitor the distance between the magnets and the guideway, and a computer regulates the strength of the current sent to the magnets to keep the gap at a constant 10 millimeters. Guidance magnets and sensors located along the sides of the frames work to keep the vehicle centered above the guideway.

Another maglev system, being developed in Japan, uses superconducting magnets to levitate and propel a train and takes advantage of both attractive and repulsive forces. The magnets are situated along the sides of the train and along the inside of a U-shaped guideway. The vehicle rolls on rubber tires until it reaches 100 kilometers per hour. An electric current then creates two opposing magnetic fields that lift the train 10 centimeters above the guideway. The array of magnets along the sides pulls and pushes the train along. Both trains provide a smooth, quiet, frictionless ride unmatched even by air flight—even though the train is literally flying above the ground.



If the train sinks too close to the guideway or drifts to one side (left), sensors send a signal to increase the magnetic attraction of the levitation and guidance magnets (right).

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TOURISM WITH A TWIST

What did I do on my summer vacation?

I could tell the story two ways: I went hiking in the rain forests of northern Queensland, Australia, peeling leeches off my legs and listening to an Aboriginal guide explain the culinary and medicinal uses of various local plants; or I went "on location," hiring a bush pilot to fly me and my son over the Tribal Council site from the cult reality television series *Survivor* and bunking in the mountain lodge where the contestants went to lick their wounds after being voted off the show.

Depending on how we describe it, the trip was either ecotourism or teletourism. Same places, same activities—different experiences. Our motherly hostess was willing to play it any way we wanted—inform us about Australian marsupials or show us snapshots of the television contestants goofing around in her kitchen.

We were embarrassed to tell our driver that we were going to Herbert River Falls because we were fans of a television series. Teletourists are often portrayed as people who just can't separate reality from fantasy. Funny—they don't say the same thing about the folks who sign up for walking tours of Dickens's London or who go to watch Shakespeare's classics performed in the re-created Globe Theatre.

Many of us see travel as a way of escaping the "fake" realms of contemporary media. I think we're lying to ourselves—tourism is all about experiencing in the flesh things we first learned about through the media.

Ecotourists ride down winding mountain roads in jeeps or on camel back, canoe along rivers, climb mountains, all in hopes of getting a glimpse of some wild animal they learned about on the Discovery Channel. Perhaps I don't enter into ecotourism with the right spirit, but as I am struggling through the Belizean underbrush, I keep humming the theme from Indiana Jones and pondering the fact that the mountain pools really are that strange deep green color they dye the water for amusement park jungle cruises. Media shapes our fantasies even when we try to escape its reach.

Often, tourism involves coming face to face with places we had previously only seen in images—and once there, we feel compelled to take our own pictures to verify the experience. Architectural critic Alvin Boyarsky describes how the picture postcard has shaped the way we view urban space, with certain generic images—the skyline at night, the vista from on top of the highest building, the juxtaposition of the old and the new—resurfacing in representations of cities around the world. When we went white-water rafting in Australia, the guides hired cameramen to run up ahead of us, perch on rocks and record our adventures so that they could be sold back to us on video when we reached our final destination. The U.S. park service has long posted signs to tell us where to point our cameras—"scenic view, 50 yards."

On the count of three, we can all grumble about how mass media has robbed us of the opportunity to have authentic experiences. But maybe we should stop beating ourselves up about all of this.

For thousands of years, pilgrims have traveled to "fabled" places—that is, places that were the subjects of stories. When in the last two millennia has any visitor had an unmediated experience of the Middle East's "Bible Lands?"

Historians tell us that many of the medieval relics and miracle stories originated as the major cities of Europe competed for visitors. Paul Bunyan turns out to be mostly "fakelore" fabricated by a Minnesota advertising man in 1914 to promote the logging industry and quickly adopted by tourist camps. Still, such stories enriched rather than impoverished our imaginations.

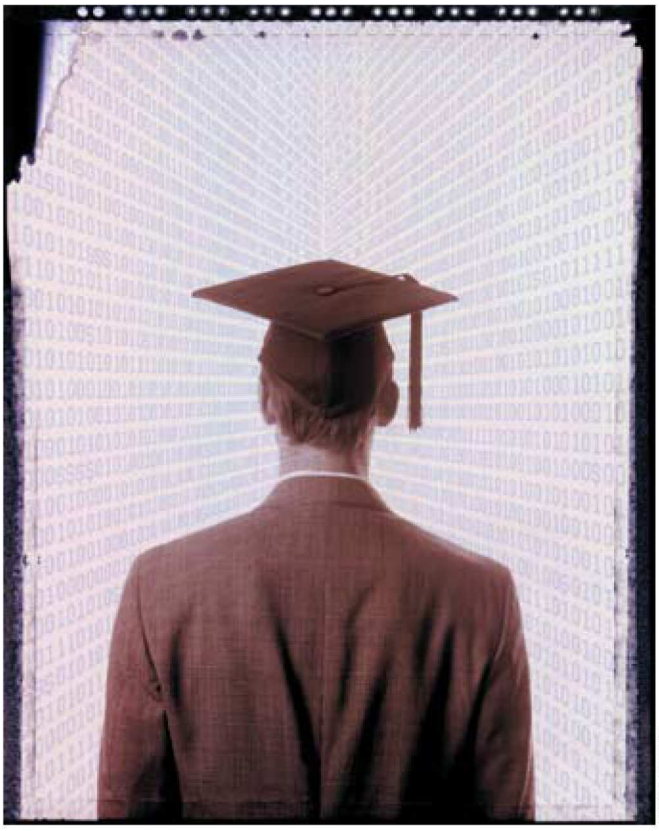
As I am struggling through the Belizean underbrush, I keep humming the theme from Indiana Jones. Media shapes our fantasies even when we try to escape its reach.

Tourism involves mapping stories onto space. Some of the stories are history, some myth; half the time, we don't care. As a rule, we value older stories over more topical ones. It's okay to stay at Lizzie Borden's house—now a bed and breakfast—but perverse to visit the Columbine massacre site. Dickens tourism is sanctified through print culture, whereas *Survivor* tourism is tainted by our conflicted feelings about television. But when tourists to Nottingham express disappointment to find that there is not much of a forest there, are their expectations shaped by folktales and ballads, children's book illustrations, Hollywood swashbucklers, or all of the above? Does it matter?

Mass media produces and reproduces stories at an alarming rate. Many of the small hotels and ranches in remote Queensland are trying to sell themselves as gateways to "Survivor Country." We all know this trend will fade in another year. In such a context, our landscape can become overpopulated with competing narrative claims. Consider, for example, the cliff that the *Survivor* contestants jumped off in one of the series' more memorable moments. On local maps, it is labeled "Butch Cassidy." So as I flew over the gorge, I was a teletourist using my camcorder to record a location that I knew from a television sequence in which contestants enacted a scene they knew from a 1969 Hollywood movie that had taken its imagery from popular pulp magazines' representations of the exploits of Wild West outlaws. Whew!

BRAVE NEW WORLD FOR HIGHER EDUCATION

Digital technologies have created the "open-source" university. BY MICHAEL SCHRAGE



STEPHEN SHEFFIELD

In April 2001, MIT president Charles M. Vest announced that the Institute would bring the "open-source" software sensibility to higher education and offer—for *free*!—its curricula and courseware to the world via the Web. This "OpenCourseWare" initiative represents a radically different approach to digitizing, marketing and globalizing education.

"OpenCourseWare looks counterintuitive in a market-driven world. It goes against the grain of current material values," said Vest at the time. "But it really is consistent with what I believe is the best about MIT." He concluded, "Simply put, OpenCourseWare is a natural marriage of American higher education and the capabilities of the World Wide Web."

Maybe it is, maybe it isn't—don't forget that marriage is hard. Still, no serious observer doubts that digital technologies are already transforming the cultures, content and economics of higher education. What's so striking, and what Vest (to his credit) so readily acknowledges, is that the technology of higher education is becoming as much a function of market mechanisms as digital media. After all, the largest single private university in America is the University of Phoenix—a decidedly for-profit institution with an enrollment north of 100,000 students whose average age is 35 and whose average annual income is $56,000. Not incidentally, nearly two-thirds of its students are women. How's *that* for diversity?

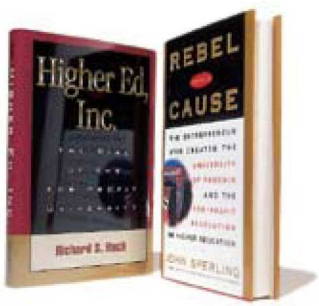
Once dismissed and derided as "diploma mills," schools like Phoenix, DeVry Institutes, Strayer University and their counterparts have already had an enormous impact on American postsecondary and postbaccalaureate education. Yes, MIT, Harvard and Berkeley are fabulous brands. But there's every reason to believe that market-oriented entities like Phoenix have every economic incentive to be even more innovative than an MIT in crafting compelling online curricula and content. A decade hence, whose "courseware" sensibilities will be educating more people faster, better and cheaper around the globe? MIT's? Or Phoenix's?

Reframe that question in an open-source context: would you rather bet on Linux (MIT) or on Windows (Phoenix) as tomorrow's dominant operating system? Or is the software world better off with both—each synergistically/antagonistically keeping the other in check?

Anyone who cares about the future of software needs to understand market trends as much as digital design. Similarly, anyone who genuinely cares about the future of higher education must accept that market forces are now as critical as technological innovation.

Rebel with a Cause by John Sperling and *Higher Ed, Inc.* by Richard S. Ruch are two stylistically different books that offer useful perspectives on these issues. The former is an intensely personal memoir of a combative entrepreneur with a University of Cambridge PhD who battled the not-for-profit academic establishment and won. The latter is a smoothly written survey by the former dean of a for-profit revealing why these schools will matter even more tomorrow than they do today. Anybody with an "elite" university education will be intrigued and provoked by these tales. Anybody who thinks that "elite" universities will be immune from the influences of these upstarts will probably have to think twice.

In *Rebel with a Cause*, Sperling does not come across as the most likable entrepreneur or educator to ever pen his memoirs. Compared to Harvard president James Bryant Conant's *My Several Lives*, or his MIT counterpart James R. Killian Jr.'s *The Education of a College President* or former MIT president Howard Wesley Johnson's recent *Holding the Center*, Sperling's book portrays him as less an academic statesman than a ruthless buccaneer, determined to topple the cozy



VITO ALUIA

incestuousness of America's higher-education establishment. He's spoiling for a fight and almost never fails to find one.

"No innovation will survive unless its protagonists are willing to respond to the inevitable attacks by the academic traditionalists with a passion of equal intensity," writes Sperling. "Furthermore, successful defense of an innovation requires will, political skill, and financial resources. [We had] all three. Plus [we were] principals who were happy warriors and who thrilled to the battle."

Don't mess with me! shrieks every other page of this business autobiography. Sperling details his battles with wives and lovers as passionately as he describes his lawsuits and lobbying of educational accreditors in states that dared interfere with his vision of adult education for the masses. Why does Sperling's vision matter? Because his business success and the rising role of Phoenix-like educational institutions gives the lie to the oft-quoted Henry Kissinger aphorism that the reason university politics are so vicious is that the stakes are so small.

Because the stakes are huge. Postbaccalaureate education, training and certification are already multibillion-dollar concerns in America. Sperling is the very model of an entrepreneur who has firsthand experience with the "inefficiencies" in the educational marketplace and knows how to exploit them. Sperling knows that quality education is often a secondary—or even a tertiary—concern of universities. After all, a university is not just a marketplace of ideas; it's a marketplace.

Will that marketplace be driven more by for-profit or not-for-profit sensibilities? (Or as Nobel Prize-winning economist Milton Friedman likes to put it, "tax-paying" versus "tax-exempt" sensibilities.) It's one thing for an MIT or a Stanford to benchmark itself against a Chicago or a Berkeley; but what does it mean to benchmark itself against a Phoenix or a DeVry? Or is that too ridiculous to even contemplate? Sperling has no (apparent) illusions about direct competition with the elite schools, because the fundamental missions are so different. But when it comes to opportunities in continuing education, distance learning and the Internet, he has no doubts about which kind of school is in the best position to profitably innovate.

MIT and Harvard are fabulous brands. But market-oriented entities like the University of Phoenix will likely be even more innovative in crafting online curricula.

To crudely oversimplify, where John Sperling is more like a Bill Gates, MIT's OpenCourseWare champions are more like open-source software's Linus Torvalds. As one looks at the rich banquet of technological opportunities, it's not at all clear which approach will have the bigger impact on educational quality.

Then again, as Ruch points out in *Higher Ed, Inc.*, the tax-paying/for-profit institution has one tremendous educational advantage over its tax-exempt/nonprofit counterpart: focus. "Lack of clarity about who is the customer continues to be a fundamental challenge for many colleges and universities.…In contrast, the for-profits do not struggle with the question of who the customer is. The customer is the student, and everyone—from the faculty to the librarians to the financial aid office to the students themselves—is clear about it."

Academic traditionalists argue that neither employers nor students should define the curricular canon. That's what professors do. What's more, true learning in higher education is contingent upon the university's research mission; it's better to drink from a running stream than a stagnant pond. Indeed, one of MIT's greatest postwar innovations was the Undergraduate Research Opportunities Program, which lets undergraduates participate in cutting-edge research alongside graduate students and professors, and which has become one of the defining fundamentals of an MIT education.

That said, it's painfully clear that many students graduate from top-tier colleges and universities with neither the domain knowledge nor critical-thinking skills they need to compete in an unforgiving job market. So they're not just looking for knowledge; they're looking for skills. They're not just looking for insights; they're thirsty for training. The rise of for-profit/tax-paying higher education is an unmistakable market signal that millions of people—and thousands of employers—are not happy with the quality of college education.

The idea that the Internet and new infrastructures for digital learning will ultimately supercede traditional universities seems silly. Then again, the success of Britain's Open University, an institute of higher education that relies on distance learning and whose graduates are as respected in British society as graduates from traditional institutions, indicates that alternative media can indeed facilitate effective learning for both traditional and nontraditional students. Ruch makes a compelling case that "marketizing" educational technology will make the for-profit schools even more influential. Don't be surprised if more and more traditional universities team up with their nontraditional counterparts to bring their curricula to the marketplace.

Indeed, as terrific as MIT's OpenCourseWare may prove to be, don't be shocked if some entrepreneur—a Media Laboratory student, perhaps, or a Sloan School alum—uses it as the core for her own startup, packaging courses in business, design and engineering, slapping on a different interface, and transforming it into a for-profit offering.

These two books affirm what MIT has always understood: the convergence of technology and entrepreneurship is what ignites creative destruction. That convergence is about to set the economics of tomorrow's higher education aflame. TR

INDEX

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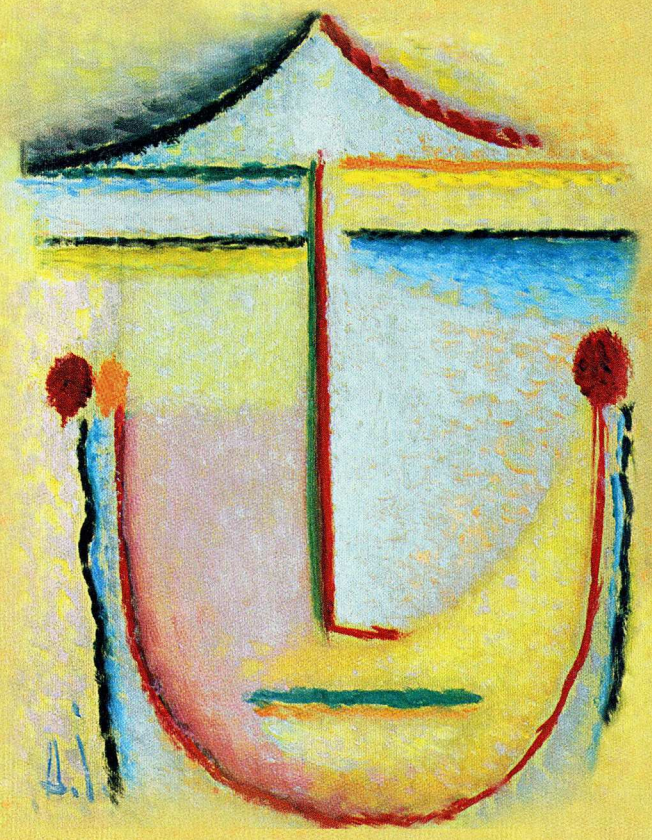

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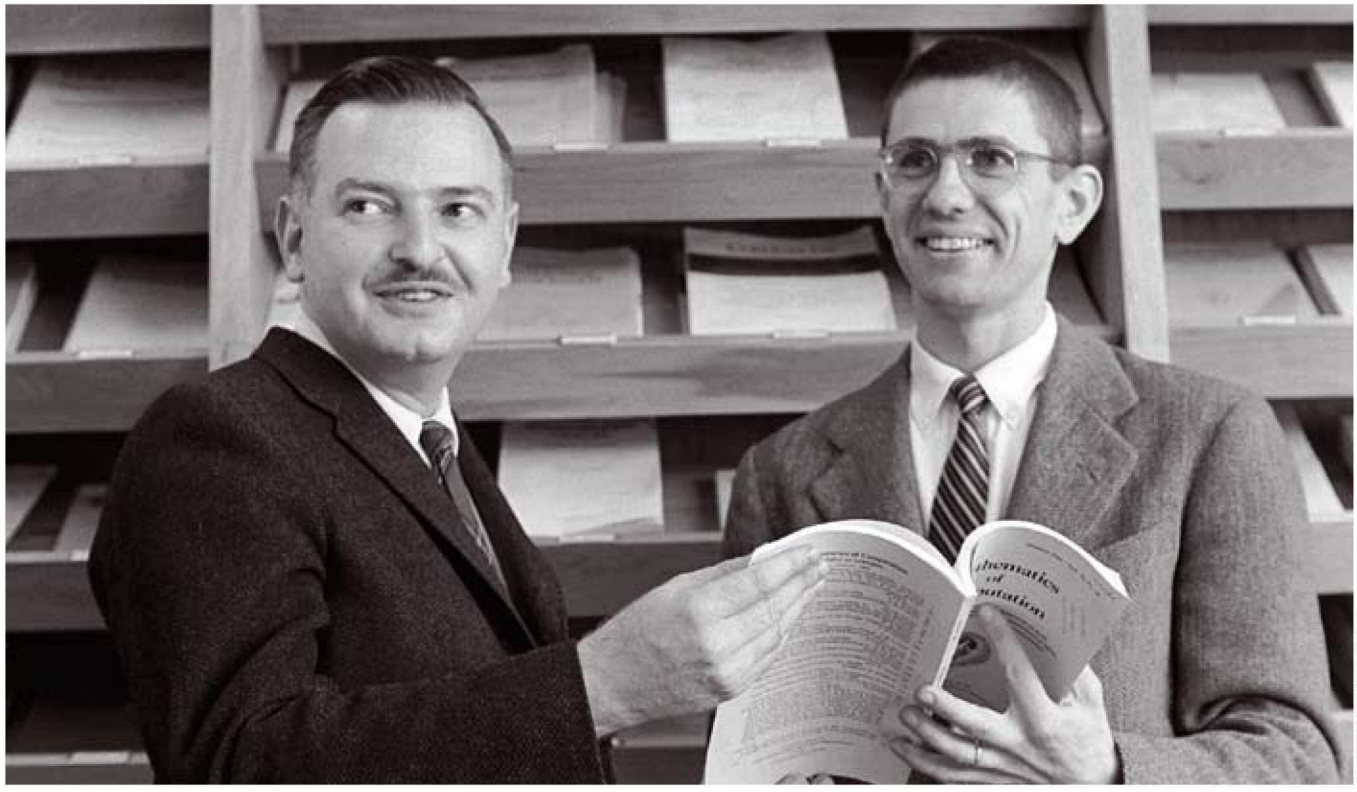

COURTESY OF DARTMOUTH COLLEGE

BACK TO BASIC

Two mathematicians set out to make programming easy—and transformed computing.

In the 1960s, most people who wanted to use computers submitted programs on punch cards to a central facility. An operator fed a batch of cards into a mainframe; users then had to wait 24 hours for a result. In 1963, Dartmouth College mathematicians John Kemeny and Thomas Kurtz *(above, left to right)* were planning a new campus computer system. Guessing that the prospect of long waits would keep students at bay, the duo devised a time-sharing system to give many students simultaneous access—and the first user-friendly programming language to go along with it. They called their new language BASIC, for Beginner's All-Purpose Symbolic Instruction Code.

Most existing computer languages, like Fortran, were crafted for engineers. Kemeny felt they were too difficult for the average person to learn, requiring months of training before a user could write an effective program. So he and Kurtz set out to create a general-purpose language that beginners could learn and start using almost immediately. Their overriding idea was to make computer programming accessible to virtually anyone. "No matter how powerful the language became," wrote Kemeny in the 1985 book *Back to BASIC*, "we never forgot the needs of beginners."

The pair started with elements of Fortran and ALGOL, a language used primarily by scientists. But they also added original features, such as line numbers, which made it easier to pinpoint and correct errors. By May 1964, both BASIC and the time-sharing system were operational. The original language had only 14 commands, and they soon found that students could begin programming after only two BASIC lessons.

Kemeny and Kurtz didn't copyright or patent their language. As a result, various versions of BASIC later became standard on early personal computers. The professors also continued to develop their original code; in 1983 they released the much-expanded True BASIC. Although huge advances in computer languages followed, BASIC lives on: this year Microsoft, whose first product was a version of BASIC for the Altair 8800 computer in 1975, will release Visual Basic .Net, a powerful cousin of BASIC updated for next-generation Web applications.

Despite this 37-year odyssey, a now retired Kurtz feels BASIC's user-friendly legacy has faded: "Sorry to say, but I don't think we had much effect." But many of today's programmers got their first exposure to computer languages through easy-to-learn BASIC—and one of them may already be working on the next revolution. TR

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